Automated Diagnosis of Coronary Artery Disease Based on Data Mining and Fuzzy Modeling

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***Abstract*—A fuzzy rule-based decision support system (DSS) is presented for the diagnosis of coronary artery disease (CAD). The system is automatically generated from an initial annotated dataset, using a four stage methodology: 1) induction of a decision tree from the data; 2) extraction of a set of rules from the decision tree, in disjunctive normal form and formulation of a crisp model; 3) transformation of the crisp set of rules into a fuzzy model; and 4) optimization of the parameters of the fuzzy model. The dataset used for the DSS generation and evaluation consists of 199 subjects, each one characterized by 19 features, including demographic and history data, as well as laboratory examinations. Tenfold cross validation is employed, and the average sensitivity and specificity obtained is 62% and 54%, respectively, using the set of rules extracted from the decision tree (first and second stages), while the average sensitivity and specificity increase to 80% and 65%, respectively, when the fuzzification and optimization stages are used. The system offers several advantages since it is automatically generated, it provides CAD diagnosis based on easily and noninvasively acquired features, and is able to provide interpretation for the decisions made.**

***Index Terms*—Coronary artery disease (CAD), data mining, decision trees, fuzzy modeling, optimization.**

I. Introduction

CORONARY artery disease (CAD) is the development of atherosclerotic plaques in coronary arteries, resulting in coronary luminal narrowing, and subsequently, occlusion, and thus leading to myocardial infarction (MI) or sudden cardiac death. The CAD is the leading cause of death in western countries. The understanding of the pathophysiology of CAD, the prevention of its development, the identification and effective modification of cardiovascular risk factors, its diagnosis and treatment in early, and reversible stages are of great importance [1]. Coronary angiography (CA) is considered to be the "gold standard" method for the diagnosis of CAD and it is widely used. However, CA is an invasive and costly procedure that needs high-level technical experience and technology and cannot be used for screening of large populations or close follow-up of treatment [2]. Therefore, other noninvasive methods are being used in the clinical setting for the diagnosis of CAD. The most popular of those include exercise electrocardiogram (ECG) [3] testing, stress echocardiography (ECHO), and single photon emission computed tomography (SPECT or scintigraphy) [4], while electron-beam computerized tomography (EBCT) or multislice spiral computerized tomography (MSCT) and coronary magnetic resonance angiography (CMRA) are also being currently used [2].

Computer-aided diagnosis methodologies have also been proposed in the literature; in this case, the data obtained by some of the aforementioned methods or other sources (i.e., laboratory examinations, demographic and/or history data, etc.) are evaluated from a computer-based application, leading to a CAD diagnosis. These methodologies can be divided into various categories, based on the type of data they use for subject characterization: 1) methods that employ the resting or exercise ECG of the patient, extracting features from it, such as the ST segment [5], [6], the QT interval [7], the T wave amplitude [8], the R wave [9], and the heart rate variability (HRV) [10]; 2) methods using medical images such as SPECT [11]–[14]; 3) methods based on heart sounds associated with coronary occlusions [15]–[18]; 4) methods based on arterio-scillography [19]; 5) methods based on Doppler ultrasound signals [20]; 6) methods employing demographic, history, and laboratory data (subject's data) [21]–[24]; and 7) methods combining more than one type of data such as ECG, scintigraphy, and subject's data [25], [26].

Some of the noninvasive methods, such as computerized tomography or magnetic resonance imaging, suffer from similar problems as CA, i.e., being costly and requiring specialized technology and expertise, while they are not widely available [2]. Most of the computer-based methods are based on the analysis of data obtained by examinations, such as stress ECHO and SPECT, which are also expensive and not widely available, but, furthermore, they suffer from technical limitations [27]. Exercise stress testing is inexpensive and widely available, but cannot be applied to all patients and has low sensitivity and specificity in the diagnosis of CAD. Cardiovascular risk factor assessment during history acquisition combined with demographic data and simple laboratory examinations may provide a measure for the

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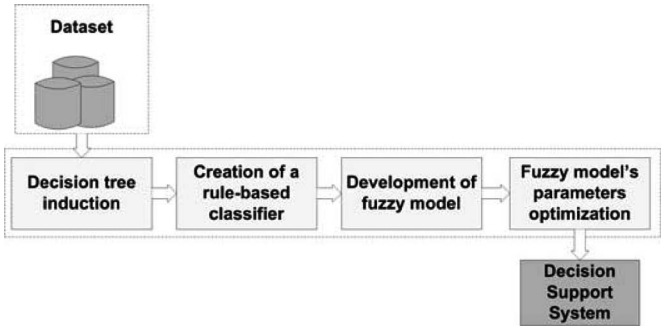

Fig. 1. Four-stage methodology used to create the DSS.

estimation of CAD risk [2]. Furthermore, the usage of arterial stiffness indices, recently proved to be related with the development of atherosclerosis [28], may improve the diagnostic procedure. Only few of the proposed computer-based methods use this type of data, i.e., subject's data that can be noninvasively and easily obtained, for the analysis. Concerning the methods used for data analysis, most of the proposed approaches are based on neural networks that cannot provide clear and direct interpretation for the decisions made. Therefore, a method able to predict noninvasively the presence of CAD using easily obtained features and providing interpretation for the decisions made would be of great clinical value.

In this paper, we propose a decision support system (DSS) [29] for the diagnosis of CAD. The DSS is automatically generated using a data-driven innovative methodology, which is implemented in four stages (see Fig 1). In the first stage, a decision tree is induced from the dataset using the C4.5 algorithm [30], while in the second stage, a set of rules is extracted from it. This set of rules is in disjunctive normal form (DNF) [31], and it formulates a crisp rule-based classifier. In the third stage, the crisp model is fuzzyfied, i.e., the crisp rules are transformed into fuzzy ones, using a fuzzy membership function instead of the crisp and S and T norms definitions, which are fuzzy equivalents of the binary OR and AND operators [32]. Finally, in the fourth stage, the parameters entering the fuzzy model are optimized using a global optimization technique [33]. The methodology is fully automated and starting from the initial annotated dataset generates a DSS, which is actually a fuzzy model with its parameters optimized subject to a specific dataset. The features that are used in the dataset are demographic and history data along with some basic laboratory examinations and indices of arterial stiffness, thus being very easily obtained. Furthermore, CA was conducted to all subjects, and their clinical statuses (presence or absence of CAD) were determined by two experienced cardiologists. The employment of fuzzy modeling is able to deal with the fuzziness, which is inherent in biomedical problems, while its combination with data mining provides the desired interpretation for the obtained decisions.

II. Materials and Methods

The four-stage methodology that is proposed for the automated creation of the DSS is presented in Fig. 1. An unknown case can be fed into the generated DSS to produce a diagnosis. The dataset and the stages of the methodology are described in detail later.

A. Dataset

The clinical data were collected in the Invasive Cardiology Department of the University Hospital of Ioannina. We included 199 subjects referred for their first CA because of suspected CAD. Patients with acute coronary syndrome, known CAD, or more than mild valvular heart disease were excluded from the study. In order to diagnose the presence or absence of CAD, CA was performed using Judkins technique. All coronary angiograms were visually assessed by two experienced angiographers and a consensus was reached. Significant CAD was defined as at least one 50% or greater diameter stenosis in at least one coronary artery vessel. The absence of CAD was defined as completely smooth epicardial coronary arteries without any narrowing visible in CA. For the total 199 subjects, 89 were normal and CAD was present in the other 110 subjects. Demographic, clinical, and vascular data were also acquired from all subjects prior to CA, while laboratory investigations from a fasting blood sample were also performed. Table I presents the 19 features selected. All patients were studied while taking regular medication (drugs were not withheld before measurements) and gave written informed consent. The study was approved by our local ethics committee.

Two demographic features were recorded: the age and sex of the patient. From the subject's history, the family history of CAD (FH), smoking history (Smok), history of diabetes mellitus (DM), and hypertension (HT) or hyperlipidaemia were used. Family history of CAD was defined as the presence of CAD in the father or brother aged <55 years or mother or sister aged <65 years. Current and ex-smokers were defined as having smoked the last cigarette less than a week and less than a year before CA, respectively. Diabetes mellitus was defined as a fasting blood glucose concentration (FBGC) ≥ 126 mg/dl or antihyperglycemic drug treatment, hypertension as systolic blood pressure (SBP) >140 mmHg, and/or diastolic blood pressure (DBP) >90 mmHg or use of antihypertensive agents, and hyperlipidemia as fasting total cholesterol >220 mg/dl or use of lipid-lowering agents (statins or fibrates). Other clinical data were also recorded; body mass index (BMI), calculated as weight (kg) divided by the square of height (square meter), waist perimeter measured in centimeter, resting heart rate (HR), measured in beats per minute (b/min), resting SBP and DBP measured in mmHg. The laboratory investigations also incorporated were creatinine (Cre), glucose (Glu), total cholesterol (Tchol), high-density lipoprotein (HDL), and triglycerides (TRG) measured in milligrams per deciliter (mg/dL). All the aforementioned features are considered to be traditional cardiovascular risk factors widely used to assess the risk of CAD. In addition, carotid–femoral pulse wave velocity (PWVcf) and augmentation index (AIx) expressed in meter per second and percentage, respectively, were also used as noninvasive indices of arterial stiffness [34], [35].

The assessment of arterial stiffness was performed noninvasively, using the Sphygmocor system [35]. Pressure waveforms

TABLE I
DATASET'S FEATURES

#	Feature	Units	Range	Mean ± stdv
1	Age	years	36-80	60.1 ± 10.03
2	Sex	male(1), female(0)	0,1	152 (1) 47 (0)
3	Family History	yes(1), no(0)	0,1	47 (1) 152 (0)
4	Smoking	smoker (2), ex-smoker (1), non-smoker (0)	0,1,2	80 (2) 40 (1) 79 (0)
5	Diabetes mellitus	FBGC ≥ 126mg/dl (1) else (0)	0,1	34 (1) 165 (0)
6	Hypertension	DBP>90mmHg and/or SBP>140mmHg (1) else (0)	0,1	118 (1) 81 (0)
7	Hyperlipidemia	total cholesterol over 220mg/dl (1) else (0)	0,1	161 (1) 38 (0)
8	Creatinine	mg/dL	0.6-3.3	0.99 ± 0.23
9	Glucose	mg/dL	37-295	110.48 ± 38.21
10	Total Cholesterol	mg/dL	128-575	222.02 ± 48.51
11	High Density Lipoprotein	mg/dL	10.6-73	39.48 ± 9.83
12	Triglyceride	mg/dL	40-690	156.87 ± 87.47
13	Body Mass Index	kg/ m^2	20.28-40.25	28.32 ± 3.36
14	Waist	cm	74-137	102.06 ± 9.62
15	Heart Rate	bpm	42-124	64.45 ± 11.63
16	Systolic Blood Pressure	mmHg	90-190	137.12 ± 19.05
17	Diastolic Blood Pressure	mmHg	50-110	81.23 ± 10.26
18	Carotid femoral pulse wave velocity	m/sec	3.5-15.5	8.9 ± 1.92
19	Augmentation Index	%	-1-61	29.56 ± 10.39

were recorded from the radial, carotid, and femoral arteries using applanation tonometry. Pulse wave velocity (PWV) was calculated as distance/transit time and was assessed by measuring both carotid–femoral arteries and carotid–radial arteries. Analysis of the central waveform allows systemic arterial stiffness to be assessed by calculating the AIx [36]. The AIx was defined as the aortic pressure divided by the pulse pressure and expressed as a percentage. The AIx is influenced by the HR [37]; therefore, an index, which normalized the AIx for 75 b/min (derived by the Sphygmocor software) was used.

B. Decision Tree Induction

The construction of the decision tree is implemented using the C4.5 inductive algorithm [30], which generates a decision tree from the training data that minimizes the expected value of the number of tests for data classification. Each internal node of the tree corresponds to a principal component, while each outgoing branch corresponds to a possible range of that component. The leaf nodes represent the class to be assigned to a sample.

The most important factor in the C4.5 algorithm is its ability to automatically select the feature, which is appropriate at each node. The feature of each node is selected in order to divide input samples effectively. The *information gain* [30] is used as a measure of effectiveness. After the induction of the decision tree, we apply a pruning method to reduce the tree's size and complexity. The two pruning methods that are often used are prepruning and postpruning [30]. In our problem, we followed the postpruning method. The postpruning tends to give better results than the prepruning since it makes pruning decisions based on a fully grown tree, unlike prepruning, which can suffer from early termination of the tree growing process. In our case, postpruning is performed by replacing a subtree with a new leaf node whose class label is determined from the majority class of records associated with the subtree (subtree replacement). The subtree replacement was performed by calculating the pessimistic error.

C. Creation of a Rule-Based Classifier

In this stage, we construct a rule-based classifier. A rule based classifier is a technique for classifying records using a collection of "if . . . then . . ." rules. The rules for the model are crisp and form the set of rules, which is represented in a DNF, $(r_1 \vee r_2 \vee \cdots r_k)$, where r_i are the classification rules or disjuncts. Each classification rule is expressed as: $r_i : (Cond_i) \rightarrow y$, where y is the predicted class. The left-hand side of the rule is the rule antecedent or precondition. It contains a conjunction of feature tests $Cond_i = (a_1 op\, \theta_1) \wedge (a_2 op\, \theta_2) \wedge \cdots \wedge (a_m op\, \theta_m)$, where (a_j, θ_j) is a feature-value (threshold) pair and op is a comparison operator chosen from the set $(=, \neq, <, >, \leq, \geq)$. Each feature test $a_j op\, \theta_j$ is a conjunct. The right-hand side of the rule is the rule consequent, which contains the predicted class y_i. A rule $r$covers a record A if the precondition of $r$matches the features of A, where $A = \{a_1, a_2, \ldots, a_{n_f}\}$ is the feature vector and n_f is the number of features characterizing a record. r is also said to be fired or triggered whenever it covers a given record. The quality of a classification rule can be evaluated using measures such as coverage and accuracy.

There are two important aspects to consider when constructing the set of rules of a rule-based classifier. First, the set of rules

should be composed by mutually exclusive rules. The rules in a set are mutually exclusive if a record triggers only one rule. This property ensures that every record is covered by at most one rule in the set. Second, the set of rules should be exhaustive. A set of rules has exhaustive coverage if there is a rule for each combination of feature values. This property ensures that every record is covered by at least one rule in the set. Together, these properties ensure that every record is covered by exactly one rule. A well-known method to construct a set of rules satisfying the earlier two aspects is to extract rules from a decision tree. The crisp set of rules is created from the final decision tree as follows.

1) One condition is created for every leaf of the tree by parsing the tree from the root node to the leaf. The tests encountered along the path form the conjuncts of the condition, while the class label at the leaf node is assigned to the rule consequent

$$Cond_i(A,\,\Theta) = c_{\rm root}(a_{\rm root},\,\theta_{\rm root}) \wedge c_j(a_j,\,\theta_j) \wedge \cdots \wedge c_k(a_k,\,\theta_k) \qquad (1)$$

where $Cond_i$ is a condition, $\Theta = \{\theta_{\rm root}, \theta_1, \theta_2, \ldots, \theta_{n_t}\}$ is a vector containing all thresholds, n_t is the total number of thresholds, a_j and θ_j are the feature and the threshold used in the conjunct j, and $c_j\,(a_j, \theta_j)$ is the respective conjunct, expressed as $c_j\,(a_j, \theta_j) = g_c\,(a_j, \theta_j)$, where g_c is the crisp membership function, defined as

$$g_c^{\rm inc}\,(a,\theta) = \begin{cases} 0, & a \le \theta \\ 1, & a > \theta \end{cases} \text{ (increasing) or}$$

$$g_c^{\rm dec}\,(a,\theta) = \begin{cases} 1, & a \le \theta \\ 0, & a > \theta \end{cases} \text{ (decreasing).} \qquad (2)$$

It should be mentioned that the number of conjuncts c_j, the features, and the thresholds that are used are different in every condition $Cond_i$ and depend on the depth of the corresponding leaf and the tests that are encountered along the path from the root to this leaf.

2) A general rule (R_y) is created for each class (y), using all the conditions $Cond_i(A,)$ having as consequent this class

$$R_y(A,\Theta) = Cond_{i_1}\,(A,\Theta) \vee Cond_{i_2}(A,\Theta) \vee \ldots Cond_{i_n}\,(A,\Theta) \qquad (3)$$

where y is the class. Therefore, the number of the general rules is the same with the number of the classes. These general rules comprise the crisp set of rules, which is exhaustive and mutually exclusive. Thus, for each feature vector A, one and only one of the general rules is true, defining its class. An example of the transformation of the decision tree to a set of crisp rules is presented in Fig. 2. The application of the first two stages (decision tree induction and creation of a rule-based classifier) to the aforementioned dataset generates a crisp set of rules. Indicative rules are shown in Fig. 3.

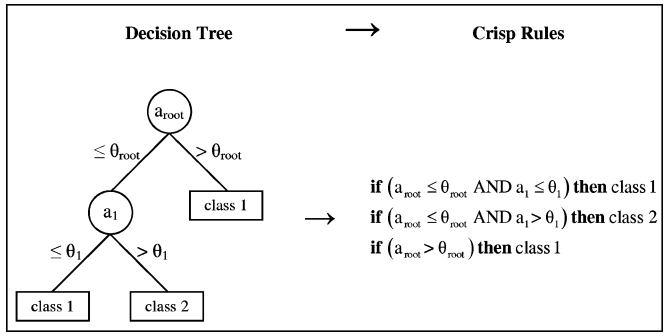

Fig. 2. Extraction of a set of crisp rules from a decision tree.

D. Development of a Fuzzy Model

The crisp set of rules is transformed into a fuzzy model using a fuzzy membership function instead of the crisp one, and fuzzy equivalents of the binary AND ($\wedge$) and OR ($\vee$) operators, which are the T and S norms [32]. In our approach, the sigmoid function, defined as

$$g_s^{\rm inc}(a,\theta_1,\theta_2) = \frac{1}{1+e^{\theta_1(\theta_2-a)}} \text{ (increasing) or}$$

$$g_s^{\rm dec}(a,\theta_1,\theta_2) = \frac{1}{1+e^{\theta_1(a-\theta_2)}} \text{ (decreasing)} \qquad (4)$$

is used as fuzzy membership function, while the T and S norms are defined as the minimum and maximum operators, respectively. Among several alternative functions that can be used for monotonic fuzzy membership function, we selected the sigmoid function since it uses only two parameters ($\theta_1,\ \theta_2$) and performs better as compared to the linear membership function (also using only two parameters) [38].

According to these, each crisp conjunct (c_j) is transformed to a fuzzy one (c_j^f) as follows: $c_j^f\,(a_j, \theta_{1,j}, \theta_{2,j}) = g_s(a_j, \theta_{1,j}, \theta_{2,j})$, and the crisp conditions are transformed to fuzzy ones as

$$Cond_i^f\,\left(A, \Theta^f\right) = \min \left\{ \begin{array}{l} c_{\rm root}^f\,(a_{\rm root}, \theta_{1,{\rm root}}, \theta_{2,{\rm root}}) \\ c_j^f\,(a_j, \theta_{1,j}, \theta_{2,j}),\ \ldots \\ c_k^f\,(a_k, \theta_{1,k}, \theta_{2,k}) \end{array} \right\} \qquad (5)$$

where $\Theta^f = \{\theta_{1,{\rm root}}, \theta_{2,{\rm root}}, \theta_{1,1}, \theta_{2,1}, \ldots, \theta_{1,n_t}, \theta_{2,n_t}\}$ is a vector containing all parameters used in the fuzzy model. Also, we define a rule evaluation metric, based on the coverage and the accuracy of the rules, in order to introduce a bias to the "stronger" rules. For this reason, the likelihood ratio is used:

$$p_i = 2\sum_{y=1}^{n_y} {\rm fr}_{i,y} \log\left(\frac{{\rm fr}_{i,y}}{e_{i,y}}\right) \qquad (6)$$

where n_y is the number of classes, ${\rm fr}_{i,y}$ is the observed frequency of class y records that are covered by a rule $Cond_i\,(A,\Theta) \rightarrow y$, and $e_{i,y}$ is the expected frequency of a rule that makes random predictions. A large p_i suggests that the number of correct predictions made by the rule is significantly larger than that expected by random guessing. Other metrics for rule evaluation could be considered; however, the metric shown in (6) was preferred since it takes into account both the accuracy and the

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IF (Sex = 0 and Smok = 0  and HR  ≤ 65 and PWVcf ≤ 10.5 and AIx ≤ 48 and FH = 0)                                          THEN  normal
IF (Sex = 0 and Smok = 0  and HR  ≤ 65 and PWVcf ≤ 10.5 and AIx ≤ 48 and FH = 1 and Tchol ≤ 240)                         THEN  normal
IF (Sex = 0 and Smok = 0  and HR  ≤ 65 and PWVcf ≤ 10.5 and AIx ≤ 48 and FH = 1 and Tchol > 240)                         THEN  CAD
IF (Sex = 0 and Smok = 0  and HR  ≤ 65 and PWVcf ≤ 10.5 and AIx > 48)                                                    THEN  CAD
IF (Sex = 0 and Smok = 0  and HR  ≤ 65 and PWVcf > 10.5)                                                                 THEN  CAD
IF (Sex = 0 and Smok = 0  and HR  > 65)                                                                                  THEN  normal
IF (Sex = 0 and Smok = 2  and Glu ≤ 94)                                                                                  THEN  CAD
IF (Sex = 0 and Smok = 2  and Glu > 94)                                                                                  THEN  normal
IF (Sex = 1 and  HR  ≤ 49)                                                                                               THEN  CAD
IF (Sex = 1 and  HR  > 49 and Age ≤ 69 and FH = 0 and DM = 0 and BMI ≤ 27.99 and TRG ≤ 191 and Age ≤ 50)                 THEN  normal
IF (Sex = 1 and  HR  > 49 and Age ≤ 69 and FH = 0 and DM = 0 and BMI > 27.99 and  HR > 53  and HDL > 27)                 THEN  normal
IF (Sex = 1 and  HR  > 49 and Age ≤ 69 and FH = 1 and HT = 0)                                                            THEN  CAD
IF (Sex = 1 and  HR  > 49 and Age ≤ 69 and FH = 1 and HT = 1 and Glu ≤ 103)                                              THEN  normal
IF (Sex = 1 and  HR  > 49 and Age ≤ 69 and FH = 1 and HT = 1 and Glu > 103)                                              THEN  CAD
IF (Sex = 1 and  HR  > 49 and Age > 69 and DM = 0)                                                                       THEN  CAD
IF (Sex = 1 and  HR  > 49 and Age > 69 and DM = 1 and Cre ≤ 1)                                                           THEN  normal
IF (Sex = 1 and  HR  > 49 and Age > 69 and DM = 1 and Cre > 1)                                                           THEN  CAD
```

Fig. 3. Indicative crisp rules.

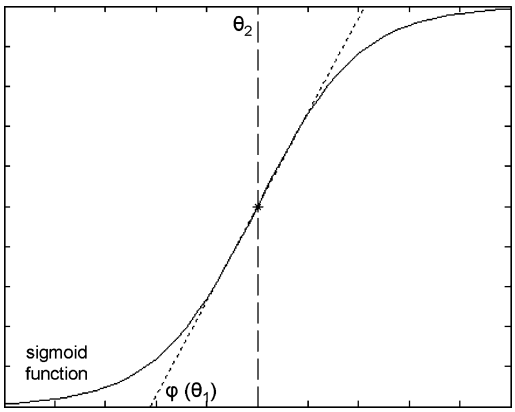

Fig. 4. Optimization parameters for the fuzzy membership function (sigmoid—increasing).

coverage of the rules. This metric is applied to each $Cond_i^f$. The general crisp rules are transformed to fuzzy ones as

$$R_y^f(A,\Theta^f) = \max\left\{\begin{array}{l} p_{i_1} \times Cond_{i_1}^f(A,\Theta^f) \\ p_{i_2} \times Cond_{i_2}^f(A,\Theta^f),\ \ldots \\ p_{i_n} \times Cond_{i_n}^f(A,\Theta^f) \end{array}\right\}. \quad (7)$$

These fuzzy general rules comprise the fuzzy model:

$$M^f\left(A,\Theta^f\right) = \arg\max_{y=1,\ldots,n_y}\left(R_y^f(A,\Theta^f)\right). \quad (8)$$

As shown in (8), for each feature vector A, the fuzzy general rule with the higher value defines its class.

E. Fuzzy Model's Parameter Optimization

The fuzzy model $M^f\left(A,\Theta^f\right)$ is optimized with respect to its parameters Θ^f, using a training dataset (D_{train}). For every conjunct, a parameter θ_1 (analogous to the slope φ) and the center θ_2 of the fuzzy membership function (sigmoid) are optimized (see Fig. 4). If X is the normalized confusion matrix

$$X_{M^f(A,\Theta^f),y} = \frac{\#\text{ of patterns in } y \text{ classified to } M^f(A,\Theta^f)}{\text{total }\#\text{ of patterns in } y} \quad (9)$$

then the cost function, used for this purpose, is defined as

$$F(\Theta, D_{\text{train}}) = \frac{\text{trace}(X)}{|D_{\text{train}}|} \quad (10)$$

The optimization method used is the healed topographical multilevel single linkage (HTMLSL) [33], a stochastic algorithm based on multilevel single linkage (MLSL). The algorithm attempts iteratively to find all local minima of an objective function $F(x)$ inside a bounded set $S \subset \mathbb{R}^n$, which are potentially global. These local minima are obtained by a local-search procedure, starting from suitably chosen points in a properly maintained sample. Stochastic algorithms in the framework of multistart suffer from the problem of recovering the same local minima repeatedly, a fact that diminishes their efficiency. The HTMLSL is constructed in such a way so as to avoid this undesirable repetition. The HTMLSL algorithm, at the kth iteration:

1) constructs a sample of points by selecting N random points from the bounded set S and evaluates at each point the objective function;
2) chooses a subset of points to be used as starting points for local searches from the earlier sample;
3) performs a local search from each starting point. If a new minimum is discovered, the algorithm stores it;
4) determines whether to stop or not, using suitable stopping criteria. If not, repeats starting from step (1);
5) from the stored local minima, the one with the lowest value is considered to be the global minimum.

III. Results

The tenfold stratified cross validation method [39] was used for evaluation. The stratification was implemented by dividing the subjects into two subsets: those with CAD and those with no CAD. The procedure was applied to each fold, generating ten different sets of crisp rules (the result after stages 1 and 2) and fuzzy models (the result after all stages). Both the crisp set of rules and the optimized fuzzy models have been evaluated. Table II presents the true positive (TP), true negative (TN), false positive (FP), and false negative (FN) results for each fold. In addition, the sensitivity (Se), specificity (Sp), and accuracy (Acc) of each fold and in overall, using gross statistics, are provided.

From the obtained results, it is clear that the last two stages (i.e., fuzzification and optimization) of the proposed methodology improved the efficiency of the crisp model generated using only the first two stages (decision tree induction and crisp model formulation). The optimized fuzzy model results to 73.4%

TABLE II
RESULTS FOR THE CRISP RULE BASED CLASSIFIER, THE PROPOSED DSS, THE ANNS, AND THE ANFIS

		Folds										Overall
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Crisp rule-based classifier	**TP**	10	6	8	5	7	7	3	10	5	7	68
	TN	6	5	4	7	4	5	4	3	5	5	48
	FP	3	4	5	2	5	4	5	6	4	3	41
	FN	1	5	3	6	4	4	8	1	6	4	42
	Se (%)	90.9	54.5	72.7	45.5	63.6	63.6	27.3	90.9	45.5	63.6	61.8
	Sp (%)	66.7	55.6	44.4	77.8	44.4	55.6	44.4	33.3	55.6	62.5	53.9
	Acc (%)	80.0	55.0	60.0	60.0	55.0	60.0	35.0	65.0	50.0	63.2	58.3
Proposed DSS ***Optimized Fuzzy model***	**TP**	9	8	11	6	10	9	9	10	8	8	88
	TN	8	5	5	8	7	6	5	4	5	5	58
	FP	1	4	4	1	2	3	4	5	4	3	31
	FN	2	3	0	5	1	2	2	1	3	3	22
	Se (%)	81.8	72.7	100	54.5	90.9	81.8	81.8	90.9	72.7	72.7	80.0
	Sp (%)	88.9	55.6	55.6	88.9	77.8	66.7	55.6	44.4	55.6	62.5	65.2
	Acc (%)	85.0	65.0	80.0	70.0	85.0	75.0	70.0	70.0	65.0	68.4	73.4
Adaptive Neuro-fuzzy Inference System	**TP**	6	6	7	6	8	5	6	8	6	6	64
	TN	5	7	4	6	5	4	5	2	4	7	49
	FP	4	2	5	3	4	5	4	7	5	1	40
	FN	5	5	4	5	3	6	5	3	5	5	46
	Se (%)	54.5	54.5	63.6	54.5	72.7	45.5	54.5	72.7	54.5	54.5	58.2
	Sp (%)	55.6	77.8	44.4	66.7	55.6	44.4	55.6	22.2	44.4	87.5	55.1
	Acc (%)	55.0	65.0	55.0	60.0	65.0	45.0	55.0	50.0	50.0	68.4	56.8
Artificial Neural Network	**TP**	9	11	7	8	9	8	8	11	10	7	88
	TN	7	4	7	7	6	6	6	4	5	7	59
	FP	2	5	2	2	3	3	3	5	4	1	30
	FN	2	0	4	3	2	3	3	0	1	4	22
	Se (%)	81.8	100	63.6	72.7	81.8	72.7	72.7	100	90.9	63.6	80.0
	Sp (%)	77.8	44.4	77.8	77.8	66.7	66.7	66.7	44.4	55.6	87.5	66.3
	Acc (%)	80.0	75.0	70.0	75.0	75.0	70.0	70.0	75.0	75.0	73.7	73.9

accuracy, improving by 15.1% the corresponding accuracy of the crisp model (58.3%). The error rates for each fold are defined as $e_{m,i} = 1 - \text{acc}_{m,i}$, where $\text{acc}_{m,i}$ is the accuracy of the model m (crisp or fuzzy) using fold i and can be approximated using normal distributions [39]. Defining $d_i = |e_{\text{fuzzy},i} - e_{\text{crisp},i}|$ as the difference between the error rates of the two models during the ith fold, then d_i is also normally distributed, with mean value d_t, which is the true difference of the error rates, and variance $\hat{\wp}^2_{d_t} = \sum_{i=1}^{k}(d_i - \bar{d})^2/(k^2 - k)$, where k is the number of degrees of freedom (i.e., number of folds) and $\bar{d} = 1/k \sum_{i=1}^{k} d_i$. In this case, the confidence interval of d_t is defined as $d_t = \bar{d} \pm t_{cl,k-1}\hat{\wp}^2_{d_t}$, where $t_{cl,k-1}$ is the t-distribution at confidence level cl and with the number of degrees of freedom k. At 95% confidence level and using ten folds, $t_{0.95,9} = 2.26$ [39], and thus, the confidence interval for the difference d_t is given as $d_t = \bar{d} \pm 2.26\ \hat{\wp}_d$. Comparing the crisp model with the fuzzy optimized model, the confidence interval for d_t at 95% confidence level is 0.15 ± 0.075, which does not span the zero value, and thus, the observed difference is statistically significant.

To compare the proposed method, we also employed two widely used classification methodologies: feed-forward artificial neural networks (ANNs) and adaptive neuro-fuzzy inference system (ANFIS) [40]. The ANNs are well known and widely used classifiers. They have proven to be very effective in many applications. On the other hand, the neuro-fuzzy techniques, such as ANFIS, have emerged from the fusion of artificial neural networks and fuzzy inference systems and form a popular framework for solving real-world problems. They combine the effectiveness and the optimization framework of the ANNs with interpretability of fuzzy inference systems. Both the ANNs and ANFIS classification methodologies were created and evaluated using the same tenfold training and test sets.

The ANNs architecture was an input layer consisting of 19 neurons (one for each of the 19 features shown in Table II), one hidden layer with 10 hidden neurons, and one output layer with a

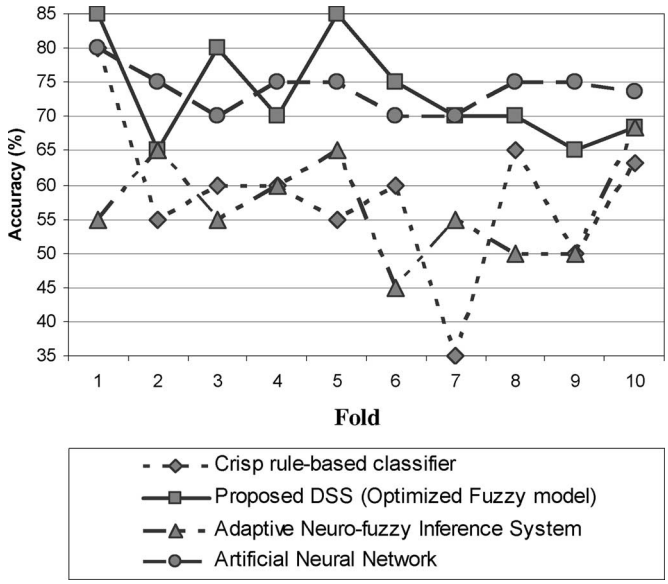

Fig. 5. Graphical representation of the obtained results presented in Table II.

single neuron. The activation functions were sigmoid functions except for the output layer, which was a linear function. The number of training epochs was set to 100, and the mean square error was used as cost function. For every fold, ten different initializations of the weights were made, and the one with the best results is reported in Table II. The ANFIS is based on a Sugeno type fuzzy system. The 19 features, described before, are used as inputs, and the fuzzy inference system is created using subtractive clustering. For optimization, the back propagation algorithm was employed, with 100 epochs. The results are presented in Table II, while a graphical representation of them is shown in Fig. 5. The results obtained from the crisp rule based classifier and the ANFIS are similar (58.3% and 56.8%, respectively), while the ANNs and the proposed DSS presented significantly better results (73.9% and 73.4%, respectively).

IV. Discussion

In this paper, we introduced a DSS for the diagnosis of CAD, which is automatically generated from a novel data-driven four-stage methodology. Initially, a set of rules is constructed from a decision tree induced by the training records, and crisp rules are extracted from this tree, forming a crisp model. Then, the crisp model is transformed to fuzzy, and, finally, the parameters of this fuzzy model are optimized. The classification results of the crisp rule-based classifier are significantly improved when it is transformed to a fuzzy model and its parameters are optimized. The improvement in accuracy ranges from 5% to 35% (see Table II) when considering each fold separately, while the overall improvement in accuracy is 15%. Furthermore, the proposed methodology reported comparable performance with the ANNs (73.4% vs. 73.9%, respectively) and significantly better results than the ANFIS.

The crisp model is based on axis-parallel decision boundaries. This is a limitation that can be treated with the fuzzyfication of the crisp rules, which introduces flexibility in the decision boundaries [41]. The fuzzy model is a generalization of the crisp model (since the parameters of the fuzzy model can be set so as to resemble the crisp model) having a larger number of parameters that can be tuned in order to create non-axis-parallel decision boundaries, which reflect the underline properties of a given dataset more accurately. The ANNs have proven to be very efficient and effective classifiers; in our problem, slightly outperformed the proposed optimized fuzzy model by 0.5%. However, the proposed approach is able to provide interpretation for its decisions, while the ANNs cannot provide clear and direct interpretation [42]. The incorporation of decision trees in the first stage of the proposed methodology bestows an advantage as compared to the ANFIS (which is a methodology having several similarities with our approach), since it provides an initialization of the fuzzy model [41]; this feature is not present in the ANFIS, thus requiring high-complexity fuzzy models in order to achieve high classification accuracy.

The proposed DSS requires only easily obtained data, such as patient's demographic and clinical data, that may derive from the patient's medical history, routine blood tests, physical examination, and noninvasive simple investigations to determine arterial stiffness. All these variables may be obtained very fast and at a low cost in an out-patient clinic, do not require special training or expertise, and, most importantly, do not expose the patient to any potential harm. All of them constitute a major advantage of the proposed DSS for CAD diagnosis. Another very important issue is the quality of the dataset. The proposed DSS is generated using a high-quality initial dataset; CA was performed to all subjects, ensuring, thus, the correctness of the final diagnosis (normal or CAD) since CA is considered to be the "gold standard" for the diagnosis of CAD.

Arterial stiffness that can be assessed noninvasively using PWVcf (i.e., PWV along the aorta) and AIx has been strongly related to atherosclerosis at various sites in the vascular tree [26] and future cardiovascular events in several patient groups [43]–[45]. The PWVcf is a simple reproducible, noninvasive measurement, which has been shown to be a reliable predictor of cardiovascular risk in end-stage renal disease [43], essential hypertension [44], diabetes, and glucose intolerance [45]. A correlation of the PWV with the extent of CAD in patients undergoing diagnostic CA has also been shown [46], [47]. The AIx is an independent predictor of all-cause, including cardiovascular, mortality in end-stage renal disease patients [48], and is also strongly and independently correlated with the presence and the extent of CAD in males, especially in younger populations [49]. However, in our dataset, these indices have not been valuable contributors in the diagnostic process. They have not been included in any of the rules derived to diagnose CAD in males, and they are only used to a limited extent in females.

Gender is the most important feature in the produced set of rules; it is used in all induced trees in the root. However, this is partially driven from the dataset since 64% of our male population (98/152) was diagnosed with CAD as compared with 25% (12/47) in the female population. Smoking has also been proven to be an important marker for CAD prediction in women; 77% of nonsmoking women did not suffer from CAD (33/42). In

TABLE III
TRADITIONAL METHODS USED IN THE CLINICAL SETTING FOR THE DIAGNOSIS OF CAD

Author	Year	Number of subject - studies	Mean age	Method	Se (%)	Sp (%)
Gianrossi [50]	1989	24074 – 147 studies (meta-analysis)		exercise ECG testing	68	77
Froelicher [51]	1998	814	58	exercise ECG testing	45	85
Fleischmann [52]	1998	44 studies (meta-analysis)		exercise ECHO / SPECT	85 / 87	77 / 64
Kim [53]	2001	82 studies (meta-analysis)		pharmacologic stress ECHO / SPECT	70 – 80 / 82 - 90	84 - 93 / 65 - 75
Imran [54]	2003	651 – 10 studies (meta-analysis)		dipyridamole ECHO / stress SPECT	70 / 88	90 / 67
Nallamothu [55]	2001	1662 – 9 studies (meta-analysis)		EBCT	80 - 92	51 - 71
Leber [56]	2005	59, stable angina	64	64-slice MSCT	73	97
Raff [57]	2005	70, suspected CAD	59	64-slice MSCT	90	95
Danias [58]	2004	993 – 39 studies (meta-analysis)		CMRA	88	56
Plein [59]	2005	102 (10 healthy / 92 with or without CAD)	31 /58	CMRA	88	82

general, the smoking history was included in almost all induced trees (excluded in only one tree). In the male population, low HR (i.e., $<=$49 beats per minute) was found to be an important predictor of CAD; this might be explained by the use of β-blockers (antianginal medications that lower HR) in subjects with very high clinical suspicion of CAD. Also, it appears that elderly males (i.e., age $>$69 years) with symptoms and signs of CAD have high probability to be diagnosed with CAD, since CAD was found in 92% (24/26) of our elderly male population. In males aged less than 69 years, family history of CAD appears to be a relatively important diagnostic feature for CAD (76% of those with positive family history had CAD, i.e., 26/34). However, some of the derived rules cannot be fully explained based on standard medical knowledge, mainly due to the data-driven nature of the proposed method, which can also discover unimportant and spurious rules.

In Table III, noninvasive methods used in the clinical setting for the diagnosis of CAD are presented. Exercise ECG testing is the most commonly used method for the diagnosis of CAD mainly because of its low cost and wide availability. However, it cannot be applied to all patients with suspected CAD (e.g., patients with disabilities) and has a relatively low sensitivity and specificity [50], [51]. Stress ECHO and scintigraphy (using exercise or pharmacological stimuli) are methods of low-to-moderate cost, as they use special technical equipment that is available in cardiological centers, and therefore, are used widely for the diagnosis of CAD and at low risk for the patient, except for scintigraphy that involves radiation and cannot be used very frequently. However, the sensitivity and specificity reported in several studies vary largely among them, explained partially by differences in stress protocols used and expertise in results' interpretation [52]–[54]. The EBCT is a method that needs highly specialized equipment, confers high radiation doses, and reveals the calcium burden of the coronary tree, thus limiting its value mainly for risk stratification and not for diagnostic purposes [55]. Finally, the MSCT and CMRA are both rapidly evolving, promising methods for the diagnosis of CAD. Despite their effectiveness, the CMRA and MSCT are methods of very high cost that require specialized equipment and highly trained personnel, and thus, with very low availability. Furthermore, they cannot be applied to a considerable percentage of patients due to several technical limitations (e.g., motion and respiratory artifacts, claustrophobia and metallic devices for the CMRA), while the MSCT involves significant radiation exposure [56]–[59]

In Table IV, we present a comparison of several computer-aided diagnosis methodologies for CAD. Again, direct comparison cannot be derived since different features and datasets have been used and also the populations vary significantly. In some of the studies, only male subjects were included [5], [6], [21], [24], while the mean age and age range of subjects that could explain differences in results is not mentioned in most of them. Our study population included patients without known CAD referred for angiography, while in some studies, subjects with previous MI or coronary artery bypass grafting (CABG) were also included [21], [23], [26]. The parameters collected and analyzed also differ among studies. In our approach, only demographic data, laboratory investigations, and indices of arterial stiffness are used; these are of low cost, easily, rapidly, and safely obtained in an out-patient basis, without the need of specially trained personnel. In [22], a subset of our dataset has been used and comparable performance has been reported, using neural networks and support vector machines. However, the employment of exercise ECG imposes a limitation to use it to patients with disabilities. The work presented in [20] attained higher sensitivity and specificity in predicting artery disease in ophthalmic or internal carotid artery by using a number of parameters obtained from the specific artery. On the contrary, we do not use only vascular data acquired from the radial, carotid, and femoral arteries, but also demographic and clinical ones, to address CAD diagnosis. It should be mentioned that most of the methods reported in Table IV are based on neural networks [13], [14], [17], [20]–[24], [26]. These methods are not able to provide clear interpretation for their decisions. On the other hand, our DSS is able to provide the desired comprehensibility since it is based on a set of rules.

However, the proposed methodology presents some limitations. The studied population was of high risk for CAD, and

TABLE IV
COMPARISON OF SEVERAL COMPUTER-AIDED DIAGNOSIS-BASED METHODOLOGIES FOR CAD DIAGNOSIS

Author	Year	Dataset				Data analysis	Results (%)		
		#	Parameters	Age	Population features		Se	Sp	Acc
Deckers et al. [5]	1988	345	Exercise ECG		Males without history of MI	Signal processing	80	90	
Akay et al. [15]	1991	20	Heart sounds	>50	Males (majority) undergoing catheterization and/or angioplasty	Signal processing	90	80	
Akay et al. [17]	1993	112	Heart sounds		Patients undergoing catheterization and/or angioplasty	Neural networks	78	89	
Akay et al. [18]	1993	73	Heart sounds		Patients undergoing catheterization and/or angioplasty	Signal processing	79	90	
Lapuerta et al. [21]	1995	162	Laboratory data (serum lipid profile)	40-59	Males with previous CABG	Neural network			66
Haddad et al. [12]	1997	100	SPECT	59±12	Subjects undergone SPECT and angiography	Case based reasoning	98	70	93
Goodenday et al. [11]	1997	42	SPECT	Average 62	31 men, 11 women. 8 patients with clinical evidence of MI	Neural network			76[1]
Kukar et al. [26]	1999	327	Subject's data, exercise ECG, SPECT		Subjects undergone exercise ECG, SPECT and angiography (many with MI)	Neural network	96	84	92
Mobley et al. [23]	2000	763	Subject's data		History of angina, MI, positive stress test	Neural network	88	68	
Frossyniotis et al. [22]	2001	139	Exercise ECG, subject's data, indices of arterial stiffness		suspected CAD	Neural network	78	75	78
Lewenstein et al. [6]	2001	776	Exercise ECG	<70	Males without history of MI		97	98	
Ebadian et al. [13]	2004	115	SPECT		Subjects undergone SPECT and angiography	Neural network	76	77	
Scott et al. [14]	2004	102	SPECT, subject's data			Neural network	88	65	
Mobley et al. [24]	2005	2004	Subject's data		Males with suspected chest pain referred for angiography	Neural network	100	26	
Pouladian et al. [19]	2005	51	Arterio-oscillography	Average 58/30/19	22 CAD/22 normal /7 with heart murmurs	Signal processing	73	90	
Guler et al. [20]	2006	169	Doppler ultrasound signals	32.5±9.1	63 healthy, 52 ophthalmic artery stenosis, 54 ocular Behcet disease	Neural network, Support vector machines	97-100	100	99
Guler et al. [20]	2006	160	Doppler ultrasound signals	32±9.6	48 healthy, 59 internal carotid artery stenosis, 53 internal carotid artery occlusion	Neural network, Support vector machines	97-98	100	98
Our study	2006	199	Subject's data, indices of arterial stiffness	36-80	suspected CAD	Data mining, fuzzy modeling	80	65	73

[1]Obtained from Table 2B of [11].

thus, the results are not representative for the general population. However, the percentage of subjects with normal vessels was rather high for high-risk population; 35,53% in males and 74,47% in females, especially as compared to other studies that report a percentage incidence of normal vessels among subjects without known CAD referred on an elective basis for their first CA. Further studies need to be performed in order to create a DSS that could accurately diagnose CAD in the general population. Also, the extension of the DSS to the determination of CAD's severity is of great interest.

V. CONCLUSION

We have presented a novel DSS for the diagnosis of CAD. The employment of easily obtained features with the interpretation ability proves the efficiency and the reliability of the method.

The obtained results indicate that the proposed optimized fuzzy model DSS improves by 15% in terms of accuracy the results of the crisp rule-based classifier, while it compares well with other widely used classification schemes such as the ANFIS and ANNs. Furthermore, the proposed DSS is automatically generated using the proposed data-driven methodology; only an initial annotated dataset is needed in order to create a DSS for a specific domain of application. This allows our methodology to be easily applied to other domains, medical or not.

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