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Decision Support Systems for Cardiovascular Diseases Based on Data Mining and Fuzzy Modelling

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INTRODUCTION

The widespread availability of new computational methods and tools for data analysis and predictive modelling requires medical informatics researchers and practitioners to systematically select the most appropriate strategy to cope with clinical prediction problems. In particular, data mining techniques offer methodological and technical solutions to deal with the analysis of medical data and construction of decision support systems. Furthermore, fuzzy modelling deals with the ambiguity inherent in all medical problems. These methods can be used to design and develop clinical decision support systems (CDSSs), which, after evaluated from the experts, can be integrated into clinical environments.

Cardiovascular diseases (CVDs) are the leading cause of death in many countries worldwide. According to the World Health Organization, CVDs are the cause of death of 16.6 million people around the globe each year. The multifaceted nature of these diseases, combined with a wide variety of treatments and outcomes, and complex relationships with other diseases, for example, diabetes, have made diagnosis and optimal

treatment of cardiovascular diseases a problem for all but experienced cardiologists.

This article addresses the decision support regarding cardiovascular diseases, using computer-based methods, focusing on the coronary artery disease (CAD) diagnosis and on the prediction of clinical restenosis in patients undergoing angioplasty. Methods reported in the literature are reviewed with respect to (i) the medical information that are employing in order to reach the diagnosis and (ii) the data analysis techniques used for the creation of the CDSSs. In what concerns medical information, easily and noninvasively-obtained data present several advantages compared to other types of data, while data analysis techniques that are characterized by transparency regarding their decisions are more suitable for medical decision making. A recently developed approach that complies with the above requirements is presented. The approach is based on data mining and fuzzy modelling. Using this approach, one CDSS has been developed for each of the two cardiovascular problems mentioned above. These CDSSs are extensively evaluated and comments about the discovered knowledge are provided by medical experts. The later is of great importance in designing

and evaluating CDSSs, since it allows them to be integrated into real clinical environments.

BACKGROUND

Data Mining is the process of discovering patterns and correlations from large amounts of data, using artificial intelligence, statistical, and mathematical techniques (Tan, Steinbach, & Kumar, 2005). Fuzzy logic is the extension of the classical crisp (binary) logic into a multivariate form. Fuzzy logic is closer to the human logic, thus being able to deal with real world noisy and imprecise data (Wang, 1986). CDSSs are computerized tools developed to assist physicians through the process of decision making. A known approach for the development of CDSSs is the use of experts' knowledge combined with an inference engine. However, recent advances in designing CDSSs employ automated knowledge extraction from data, using data mining techniques, while fuzzy logic provides several advantages in designing inference engines, compared to the classical crisp logic. The combination of data mining and fuzzy modelling provides a powerful tool for fully automated creation of CDSSs, experiencing several advantages: (i) transparency in decision making, (ii) addressing the ambiguity inherent in clinical data, and (iii) ability to interpret all decisions in a medical manner. All the above are of great importance for physicians, when performing decision making.

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 or sudden cardiac death. 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 (Escolar, Weigold, Fuisz, & Weissman, 2006). Computer aided methodologies for CAD diagnosis have also been proposed in the literature; in this case the data obtained by some of the above mentioned methods or other sources (i.e., laboratory examinations, demographic, and/or history data, etc.) are evaluated by 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. Several methods are based on heart sounds associated with coronary occlusions (Akay & Welkowitz, 1993). Also, methods which employ the resting or exercise electrocardiogram (ECG) of the patient, extracting features from it, like the R wave (Szildgyi, Szildgyi, & David, 1997), the QT interval (Ng, Wong, Mora, Passariello, & Almeida, 1998), the T wave amplitude (Sabry-Rizk et al., 1999), the heart rate variability (Tkacz & Kostka, 2000), and the ST segment (Lewenstein, 2001) have been proposed. Furthermore, there are methods using medical images, such as SPECT (Haddad, Adlassnig, & Porenta, 1997), and methods based on arterio-scillography (Pouladian, Golpayegani, Tehrani-Fard, & Bubvay-Nejad, 2005). There exist also methods that employ demographic, history, and laboratory data (Frossyniotis et al., 2001; Mobley, Schechter, Moore, McKee, & Eichner, 2005; Tsipouras et al., 2006) and methods that combine more than one type of data (Kukar, Kononenko, Groselj, Kralj, & Fettich, 1999; Scott, Aziz, Yasuda, & Gewirtz, 2004).

The evolution and widespread adoption of percutaneous transluminal coronary angioplasty (PTCA) represents a major advance in the management of acute coronary syndromes, resulting in a significant reduction in early and late mortality compared to pharmacologic reperfusion therapy. Coronary artery restenosis remains a major limitation of PTCA and is usually defined as $\geq 50\%$ stenosis in the treated segment at follow up, or at least 50% loss of the original gain in the minimal luminal diameter. Many clinical, angiographic, and procedural features have been studied as predictors for restenosis but it has proven difficult to stratify patients with regard to the risk of restenosis. Knowledge of risk factors for restenosis may help to refine indications of PTCA, reduce the frequency of restenosis, and select optimal candidates for a PTCA procedure. Despite lowering the restenosis rate with the implantation of coronary stents, it occurs in approximately 12-60% of the patients within 6 months after intervention depending mainly on the patients' and procedural characteristics. Computer aided methodologies for the prediction of clinical restenosis have also been proposed in the literature. These can be divided into two categories, regarding the data they use for the analysis: methods that employ only CAD risk factors such as demographic, history, and clinical data (Budde, 1999; Tsipouras et al., 2006) and methods that combine CAD risk factors with angiographic features (Maier, Mini, Antoni, Wischniewski, & Meier, 2001; Resnic, Popma, Ohno-Machado, 2000).

CDDSS FOR CARDIOVASCULAR DISEASES

A recently developed method for automated CDDSSs creation is based on data mining and fuzzy modeling (Tsipouras et al., 2006). Specifically, in order to create the CDDSS, a three stage methodology is used: (i) creation of a rule-based classifier using data mining techniques, (ii) development of a fuzzy logic model, and (iii) optimisation of the fuzzy logic model's parameters. Briefly, in the first stage, a set of crisp rules is generated. This is performed by inducing a decision tree from a training dataset and then transforming the tree into a set of rules. In the second stage, the crisp set of rules is transformed to a fuzzy set of rules, using a membership function instead of the crisp ones and S and T norms instead of the binary AND and OR operators. Finally, in the third stage, all thresholds and parameters involved in the fuzzy model are optimized with respect to a training dataset. The fuzzy model with the optimized parameters comprises the final CDDSS. To apply the above methodology in a specific domain, an annotated dataset is required. The quality of this dataset is very important for developing an effective CDDSS. This methodology has been used in order to create CDDSSs for CAD diagnosis and prediction of clinical restenosis in patients undergoing angioplasty.

Application to CAD Diagnosis

The dataset used for CAD diagnosis included 199 subjects suspected of having CAD and who underwent coronary angiography for the first time. Patients with known CAD were excluded from the study. Of the subjects, 89 had normal angiograms and in the remaining 110 subjects the presence of CAD was confirmed by two experts. In order to characterise each subject, 19 features (shown in Table 1) were used. Two demographic features were recorded: the age and sex of the patient. From the subject's history data, the family history of CAD, smoking history, history of diabetes mellitus, and measurements of hypertension or hyperlipidaemia were used. The incorporated laboratory investigations were creatinine, glucose, total cholesterol, high density lipoprotein, and triglycerides. In addition, Carotid-Femoral Pulse Wave Velocity and Augmentation index were also used as non-invasive indices of arterial stiffness (Van Bortel et al., 2002; Woodman & Watts, 2003). In order to confirm the presence or absence of CAD,

coronary angiography was performed by the Judkins technique. All coronary angiograms were visually assessed by two experienced cardiologists to reach consensus agreement. Significant CAD was defined as at least one stenosis of 50% or greater diameter in at least one coronary artery vessel. The absence of CAD was defined as completely smooth epicardial coronary arteries.

In Figure 1 an indicative set of rules is presented. These rules are extracted using data mining and (before fuzzification) were commented by the experts. According to the experts, gender is the most important feature in the produced set of rules. 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 non smoking women did not suffer from CAD (33/42). 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 non important and spurious rules.

In Table 2, several computer aided diagnosis methodologies for CAD are presented. Some of the non-invasive methods, such as computerized tomography or magnetic resonance imaging, suffer from similar problems as CA, that is, being costly and requiring specialized technology and expertise, while they are not widely available (Escolar et al., 2006). 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, not widely available, and suffer from technical limitations (Merz, 2005). 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.

Table 1. Features for CAD CDSS

#	Feature	Units
1	Age	Years
2	Sex	male(1), female(0)
3	Family History (FH)	yes(1), no(0)
4	Smoking (Sm)	smoker (2), ex-smoker (1), non-smoker (0)
5	Diabetes mellitus (DM)	FBGC \geq 126mg/dl (1) else (0)
6	Hypertension (HT)	DBP>90mmHg and/or SBP>140mmHg (1) else (0)
7	Hyperlipidemia (HL)	total cholesterol over 220mg/dl (1) else (0)
8	Creatinine (Cre)	mg/dL
9	Glucose (Glu)	mg/dL
10	Total Cholesterol (TC)	mg/dL
11	High Density Lipoprotein (HDL)	mg/dL
12	Triglyceride (TG)	mg/dL
13	Body Mass Index (BMI)	kg/ m ²
14	Waist	Cm
15	Heart Rate (HR)	Bpm
16	Systolic Blood Pressure (SBP)	mmHg
17	Diastolic Blood Pressure (DBP)	mmHg
18	Carotid femoral pulse wave velocity (PWVcf)	m/sec
19	Augmentation Index (AIx)	%

The populations and the parameters collected and analyzed differ among studies; in some of the studies, only male subjects (Lewenstein, 2001; Mobley et al., 2005) or subjects with previous myocardial infarction (MI) or coronary artery bypass grafting (CABG) (Kukar et al., 1999), were included. It should be mentioned that most of the methods reported in Table 2 are based on neural networks (Akay & Welkowitz, 1993, Frossyniotis et al., 2001; Kukar et al., 1999; Mobley et al., 2005; Scott et al., 2004). These methods are not able to provide clear interpretation for their decisions.

Application to Prediction of Clinical Restenosis in Patient Undergoing Angioplasty

The dataset used for prediction of clinical restenosis in patients undergoing angioplasty consisted of 1,000 subjects that underwent angioplasty. In order to characterise the subjects, the 15 features shown in Table 3 were used. Family history, hypertension, diabetes mellitus, current smoking, and hyperlipidemia were defined as for the CAD CDSS. Clinical presentation of CAD was classified as unstable angina, stable angina,

Table 2. Comparison of several computer aided methodologies for CAD diagnosis

Author – Year	Number of subjects	Method – analysis	Se (%)	Sp (%)	Acc (%)
Akay & Welkowitz, 1993	112	Heart sounds – Neural network	78	89	
Haddad et al., 1997	100	SPECT – Case based reasoning	98	70	93
Kukar et al., 1999	327	Subject's data, exercise ECG, SPECT – Neural network	96	84	92
Frossyniotis et al., 2001	139	Exercise ECG, subject's data, indices of arterial stiffness – Neural network	78	75	78
Lewenstein, 2001	776	Exercise ECG	97	98	
Scott et al., 2004	102	SPECT, subject's data – Neural network	88	65	
Mobley et al., 2005	2004	Subject's data – Neural network	100	26	
Pouladian et al., 2005	51	Arterio-oscillography – signal processing	73	90	
Tsipouras et al., 2006	199	Subject's data, indices of arterial stiffness – data mining, fuzzy modelling	80	65	73

or acute myocardial infarction. The vessels treated with angioplasty were the right coronary artery, left main stem, left anterior descending artery, left circumflex artery, and bypass grafts. The patients underwent either angioplasty with balloon alone or balloon followed by stenting with a noncoated metal stent. All patients were followed up for at least 12 months. The composite end point of the study was clinical restenosis manifested as cardiac death, a new non fatal myocardial infarction or a new revascularisation attempt of the stented vessel in less than 6 months after the initial angioplasty procedure.

In Figure 2, some indicative rules are presented. The experts agree that the most important feature in the production of rules for the prediction of clinical restenosis is the number of diseased coronary vessels since 15.4% (i.e., 87/565) of the multivessel cases presented with restenosis in less than 6 months after the percutaneous coronary intervention (PCI) procedure in contrast to only 7.9% (i.e., 29/365) of the single vessel patients. Patients who underwent the angioplasty in a stable condition (i.e., stable angina) had probably a favourable prognosis (only 8.3% of patients with stable angina presented with restenosis in less than 6 months compared to 13.5% of those with unstable

coronary syndromes), except perhaps for older (i.e., > 65 years old) or diabetic people. On the other hand, unstable coronary syndromes (i.e., unstable angina and myocardial infarction) are related to worse prognosis in terms of clinical restenosis even in younger ages (i.e., 55 years old) or patients without many severe cardiovascular risk factors. History of a previous PCI procedure and especially history of coronary aortic bypass surgery (occurrence of restenosis in 19.4% of patients with previous CABG compared to 12.2% without CABG history) are associated with increased risk of restenosis after coronary angioplasty. However, some of the derived rules could not be explained based on current medical knowledge on various interactions among the features used in our models.

In Table 4, a comparison of several computer-aided methodologies for the prediction of clinical restenosis is presented. Different datasets were used in each method; therefore a direct comparison is not feasible. Some approaches (Budde, 1999; Tsipouras et al., 2006) are based on noninvasively acquired data, while others employ also data obtained from angiographies (Maier et al., 2001; Resnic et al., 2000), thus being invasive approaches. Data analysis is performed mainly using rule based systems (Budde, 1999, Maier et al., 2001,

Figure 1. Indicative rules (crisp) for CAD diagnosis

IF (Sex = 0 and Sm = 0 and HR ≤ 65 and PWVcf ≤ 10.5 and Aix ≤ 48 and FH = 0)	THEN	normal
IF (Sex = 0 and Sm = 0 and HR ≤ 65 and PWVcf ≤ 10.5 and Aix ≤ 48 and FH = 1 and TC ≤ 240)	THEN	normal
IF (Sex = 0 and Sm = 0 and HR ≤ 65 and PWVcf ≤ 10.5 and Aix ≤ 48 and FH = 1 and TC > 240)	THEN	CAD
IF (Sex = 0 and Sm = 0 and HR ≤ 65 and PWVcf ≤ 10.5 and Aix > 48)	THEN	CAD
IF (Sex = 0 and Sm = 0 and HR > 65 and PWVcf > 10.5)	THEN	CAD
IF (Sex = 0 and Sm = 2 and Glu ≤ 94)	THEN	normal
IF (Sex = 0 and Sm = 2 and Glu > 94)	THEN	CAD
IF (Sex = 1 and HR ≤ 49)	THEN	normal
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	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

Figure 2. Indicative rules (crisp) for prediction of clinical restenosis

IF (SVD = 1 and CP = 1 and VT = 1 and FH = 0 and HL = 1 and PTCA = 0)	THEN	normal
IF (SVD = 1 and CP = 1 and VT = 1 and FH = 0 and HL = 1 and PTCA = 1)	THEN	restenosis
IF (SVD = 1 and CP = 1 and VT = 1 and FH = 1 and ST = 1)	THEN	normal
IF (SVD = 1 and CP = 1 and VT = 2)	THEN	normal
IF (SVD = 1 and CP = 1 and VT = 3 and Age ≤ 66)	THEN	normal
IF (SVD = 1 and CP = 2 and CABG = 0 and HL = 0 and HT = 0)	THEN	normal
IF (SVD = 1 and CP = 2 and CABG = 1)	THEN	restenosis
IF (SVD = 1 and CP = 3)	THEN	normal
IF (SVD = 0 and CP = 1 and PTCA = 0 and VT = 1 and CABG = 0 and Age ≤ 51)	THEN	normal
IF (SVD = 0 and CP = 1 and PTCA = 0 and VT = 2 and Sm = 0 and HT = 0 and Age > 60)	THEN	restenosis
IF (SVD = 0 and CP = 1 and PTCA = 0 and VT = 3 and ST = 1 and FH = 0 and Age ≤ 58)	THEN	restenosis
IF (SVD = 0 and CP = 2 and Sex = 0 and VT = 3 and DM = 0 and ST = 2)	THEN	restenosis
IF (SVD = 0 and CP = 2 and Sex = 0 and VT = 3 and DM = 1)	THEN	restenosis
IF (SVD = 0 and CP = 2 and Sex = 1 and PTCA = 1)	THEN	restenosis
IF (SVD = 0 and CP = 3 and HT = 0 and FH = 0 and ST = 1 and Age ≤ 66)	THEN	normal
IF (SVD = 0 and CP = 3 and HT = 0 and FH = 0 and ST = 1 and Age > 66)	THEN	restenosis
IF (SVD = 0 and CP = 3 and HT = 1 and Sm = 0 and PTCA = 0 and Sex = 1 and DM = 0)	THEN	normal
IF (SVD = 0 and CP = 3 and HT = 1 and Sm = 0 and PTCA = 0 and Sex = 1 and DM = 1)	THEN	restenosis

Table 3. Features for prediction of clinical restenosis CDSS

#	Feature	Units
1	Stent Type (ST)	Balloon (0), Bare Metal Stent (1), Drug Eluting Stent (2)
2	Sex	male(1), female(0)
3	Age	Years
4	Diabetes Melitus (DM)	FBGC \geq 126mg/dl (1) Else (0)
5	Hypertension (HT)	DBP>90mmHg and/or SBP>140mmHg (1) else (0)
6	Smoking (Sm)	smoker (1), non-smoker (0)
7	Hyperlipidemia (HL)	total cholesterol over 220mg/dl (1) else (0)
8	Family History (FH)	yes(1), no(0)
9	CAD History (CAD)	yes(1), no(0)
10	Prior PTCA (PTCA)	yes(1), no(0)
11	Prior CABG (CABG)	yes(1), no(0)
12	Single Vessel Disease (SVD)	yes(1), no(0)
13	Clinical Presentation (CP)	Unstable angina (1), Acute myocardial infarction (2), Stable angina (3)
14	Vessel Treated (VT)	Left anterior descending (1), Left circumflex (2), Right coronary artery (3), Left main (4), Bypass graft (5)
15	IIB/IIIA	yes(1), no(0)

Table 4. Comparison of several computer aided methodologies for prediction of restenosis after coronary angioplasty

Author - Year	Number of subjects	Data	Method	Accuracy (%)
Budde, 1999	2500	Risk factors for CAD	Rule based system	95
Resnic et al., 2000	2804	Demographic, clinical and angiographic data	Statistical analysis	81
			Risc score	79
			ANN	81
Maier et al., 2001	325 (lesions)	Clinical and angiographic data	Statistical analysis	58
			Rule based system	92
Tsipouras et al., 2006	1000	Demographic, history and clinical data	Data mining, fuzzy modelling	61

Tsipouras et al., 2006) or artificial neural networks (Resnic et al., 2000).

FUTURE TRENDS

Researchers have spent great efforts in the design and development of CDSSs for several domains in medicine and health care. Most of the CDSSs try to reduce the effort and time of the experts when performing diagnosis. However, a plethora of systems has been presented for staging, treatment, dose adjustment, and follow-up. An important requirement of this type of system is the transparency regarding the automated decisions and the interpretation they provide. Moreover, experts rely more on systems that their automated decisions coincides with established medical knowledge. Integration of knowledge provided by the experts and knowledge generated using data mining methods, for the creation of more sophisticated CDSSs, is the trend of the future. Established medical knowledge combined with data mining models is the key to increase the effectiveness of these systems and provide advanced tools for computer based clinical medicine.

CONCLUSION

CVDs are among the most life threatening diseases worldwide. A vast amount of patients suffering from CVDs are examined, hospitalized, and treated every day; this has a major impact in national health care systems. The importance of CVDs has led to the development of a large number of computer-based CDSSs that mainly focus in diagnosis, treatment, or follow-up. An important requirement of a CDSS is its ability to provide transparency regarding the generated decisions, thus providing a clear insight of their inner process for decision making; this is essential for physicians in order to incorporate such systems in their clinical practice. Another important requisite is an extensive evaluation of a CDSS by medical experts, in order to comment on the functionality of the system and fully exploit its potential. Furthermore, the employment of easily obtained and noninvasive features for decision support is considered an advantage since it facilitates the straightforward application of the system. Most of the CDSSs proposed in the literature do not meet these requirements, thus complicating their application in

clinical practice. The CDSSs presented in this article fulfill these issues, making them suitable to be used in clinical practice.

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KEY TERMS

Artificial Neural Network: An interconnected group of artificial neurons that uses a mathematical or computational model for information processing based on a connectionist approach to computation.

Clinical Decision Support Systems (CDSS): Computer based methods that aim to assist clinicians in decision making. The core of CDSSs is an inference engine that can generate case specific advice based on medical data.

Clinical Restenosis: Death presumably from cardiac causes, myocardial infarction not attributable to another coronary artery than the target vessel, and target vessel revascularization either by repeat PTCA or CABG.

Coronary Artery Disease: The narrowing of the coronary arteries, sufficiently to prevent adequate blood supply to the heart muscle. It is usually caused by atherosclerosis and may progress to the damage of heart muscle.

Data Mining: The process of extracting previously unknown and potentially useful knowledge, hidden in large volumes of data.

Fuzzy Logic: A way of reasoning that can cope with uncertain or partial information.

Inference Engine: The part of a decision support system that performs the reasoning function.