AtherEx: An Expert System for Atherosclerosis Risk Assessment

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Abstract. A number of calculators that compute the risk of atherosclerosis has been developed and made available on the Internet. They all are based on computing weighted sum of risk factors. We propose instead to use more flexible expert systems to estimate the risk. The goal of the AtherEx expert system is to classify patients according to their atherosclerosis risk into four groups. This application is based on the Nest rule–based expert system shell. Knowledge for the AtherEx was obtained (using the machine learning algorithm KEX) from the data concerning a longitudial study of atherosclerosis risk factors and further refined by domain expert. AtherEx is available for consultations on web.

1 Introduction

Atherosclerosis is a slow, complex disease that typically starts in childhood and often progresses when people grow older. In some people it progresses rapidly, even in their third decade. Many scientists think it begins with damage to the innermost layer of the artery. Atherosclerosis involves the slow buildup of deposits of fatty substances, cholesterol, body cellular waste products, calcium, and fibrin (a clotting material in the blood) in the inside lining of an artery. The buildup (referred as a plaque) with the formation of the blood clot (thrombus) on the surface of the plaque can partially or totally block the flow of blood through the artery. If either of these events occurs and blocks the entire artery, a heart attack or stroke or other life-threatening events may result. People with a family history of premature cardiovascular disease (CVD) and with other risk factors of atherosclerosis have an increased risk of the developing of atherosclerosis. Research shows the benefits of reducing the controllable risk factors for atherosclerosis:

– high blood cholesterol (especially LDL or "bad" cholesterol over 100 mg/dL),
– cigarette smoking and exposure to tobacco smoke,
– high blood pressure (blood pressure over 140/90 mm Hg),
– diabetes mellitus,
– obesity (Body Mass Index BMI over 25),
– physical inactivity.

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Table 1. Calculators of CVD Risk

system	knowledge source	no. of questions	suitable for	results
NCEP ATP III	ATP III Guidelines	11 + 2	all patients	CVD risk in 10 years
Risk assesment tool	Framingham study	4 + 2	all patients	IM risk in 10 years
Framingham Risk Assessment	Framingham study	5 + 2	all patients	IM risk in 10 years
PROCAM Risk Calculator	PROCAM study	6 + 3	middle-aged men	IM risk in 10 years
PROCAM Risk Score	PROCAM study	7 + 4	middle-aged men	IM risk or death on CVD in 10 years
PROCAM Neural Net	PROCAM study	11 + 5	middle-aged men	IM risk in 10 years
Heart Score	European Society of Cardiology	4 + 2	middle-aged patients	death on CVD in 10 years

Atherosclerosis-related diseases are a leading cause of death and impairment in the United States, affecting over 60 million people. Additionally, 50% of Americans have levels of cholesterol that place them at high risk for developing coronary artery disease. Similar situation can be observed in other countries. So the education of patients about prevention of atherosclerosis is very important.

A number of calculators that compute the risk of atherosclerosis, CVD or myocardial infarction (IM) has been developed and made publicly available on the Internet. These systems usually ask questions about life style (typically about smoking habits) and about results of examination and laboratory tests (typically about blood pressure and cholesterol level) and then compute a risk that given person will suffer from atherosclerosis in 10 years. The computation has a form of weighted sum of used risk factors. The exact formula is based on different knowledge sources: the *NCEP ATP III* system [8] is based on the Adult Treatment Program III guidelines issued by the US National Heart, Lunge and Blood Institute (NHLBI) within the National Cholesterol Education Program (NCEP), the *Risk Assessment Tool* [11] also from NHLBI is based on the data collected within the Framingham Heart Study performed in U.S. - the same study is behind the *Framingham Risk Assessment calculator* [4]. The prospective cardiovascular Münster study (PROCAM) is the background for the *PROCAM Risk calculator* [9] and the *PROCAM Risk score* [10] systems developed in Germany. The *Heart Score* system [7] developed by the European Society of Cardiology is based on data from 12 European cohort studies covering a wide geographic spread of countries at different levels of cardiovascular risks. Tab. 1 summarizes some further information about these systems[1].

[1] The column `no. of questions` gives the number of questions on life style (first number) and the number of lab. tests (second number).

The main drawback of using these calculators by an un-experienced user is the necessity to give exact answers to all questions (including questions about values of results of laboratory tests). We believe, that expert systems due to their flexibility and capability to process uncertain or missing information can overcome this obstacle and thus are more suitable for the task of atherosclerosis risk assessment by a non-expert user.

The rest of the paper is organized as follows: section 2 provides a review of the features of NEST with respect to knowledge representation and inference mechanism, section 3 describes the atherosclerosis risk assessment application of NEST (the knowledge acquisition and implementation), and section 4 gives a summary and some future perspectives of the system.

2 Expert System NEST

Expert systems (ES) are typically defined as computer systems that emulate the decision-making ability of a human expert. The power of an ES is derived from presence of a *knowledge base* filled with expert knowledge, mostly in symbolic form. In addition, there is a generic problem-solving mechanism used as *inference engine* [5]. The research in the area of expert systems started in mid-70s, classical examples of early systems that influenced other researchers are MYCIN and PROSPECTOR. The central point of these systems was the *compositional* approach to inference, allowing to compose the contributions of multiple rules (leading to the same conclusion) using a uniform combination function, regardless their mutual dependencies. This approach has later been subject to criticism by most of the uncertainty-processing community. In the design of NEST [3], we attempted to partially overcome the problem that represented the most severe hindrance to compositional system deployment: limited expressiveness of proposition-rule networks for real-world modeling purposes.

2.1 Knowledge Representation

NEST uses attributes and propositions, rules, integrity constraints and contexts to express the task-specific (domain) knowledge.

Four types of attributes can be used in the system: binary, single nominal, multiple nominal, and numeric. According to the type of attribute, the derived propositions correspond to:

- values `True` and `False` for a *binary* attribute.
- each value for a *nominal* attribute. The difference between single and multiple nominal attribute is apparent only when answering the question about value of the attribute.
- fuzzy intervals for a *numeric* attribute. Each interval is defined using four points; fuzzy lower bound (FL), crisp lower bound (CL), crisp upper bound (CU), fuzzy upper bound (FU). These values need not to be distinct; this allows to create rectangular, trapezoidal and triangular fuzzy intervals.

Rules are defined in the form

$$condition \Rightarrow conclusion(weight), action$$

where *condition* is disjunctive form (disjunction of conjunctions) of literals (propositions or their negations), *conclusion* is a list of literals and *action* is a list of actions (external programs). We distinguish three types of rules:

– *compositional* - each literal in conclusion has a weight which expresses the uncertainty of the conclusion if the condition holds with certainty. The term compositional denotes the fact, that to evaluate the weight of a proposition, **all** rules with this proposition in the conclusion are evaluated and combined.
– *apriori* - compositional rules without condition; these rules can be used to assign implicit weights to goals or intermediate propositions,
– *logical* - non-compositional rules without weights; only these rules can infer the conclusion with the weight `true` or `false`. **One** activated rule thus fully evaluates the proposition in conclusion.

A list of actions (external programs) can be associated with each rule. These programs are executed if the rule is activated.

As additional knowledge base elements we introduced *integrity constraints* allowing to detect inconsistent patterns of weights and *contexts* that are used to condition the evaluation of attributes or rules.

2.2 Inference Mechanism

During consultation, the system uses rules to compute weights of goals from the weights of questions. This is accomplished by (1) selecting relevant rule during current state of consultation, and (2) applying the selected rule to infer the weight of it's conclusion.

1. The selection of relevant rule can be done using either backward or forward chaining. The actual direction is determined by the user when selecting the consultation mode (see later).
2. For rules with weights (compositional and apriori ones), the system combines contributions of rules using compositional approach described in nest subsection. For rules without weights, the system uses non-compositional approach based on (crisp) modus ponens – to evaluate the weight of a conclusion, and (crisp) disjunction – to evaluate a set of rules with the same conclusion.
The weights are propagated not only towards the actual goal but by using all rules applicable at given moment.

Uncertainty processing. in NEST is based on the algebraic theory of P. Hájek [6]. This theory generalizes the methods of uncertainty processing used in the early expert systems like MYCIN and PROSPECTOR. Algebraic theory assumes that the knowledge base is created by a set of rules in the form

$$condition \Rightarrow conclusion(weight)$$

where *condition* is a conjunction of literals, *conclusion* is a single proposition and *weight* from the interval $[-1, 1]$ expresses the uncertainty of the rule.

During a consultation, all relevant rules are evaluated by combining their weights with the weights of conditions. Weights of questions are obtained from the user, weights of all other propositions are computed by the inference mechanism. Five combination functions are defined to process the uncertainty in such knowledge base:

1. $NEG(w)$ - to compute the weight of negation of a proposition,
2. $CONJ(w_1, w_2, ..., w_n)$ - to compute the weight of conjunction of literals,
3. $DISJ(w_1, w_2, ..., w_n)$ - to compute the weight of disjunction of literals,
4. $CTR(a, w)$ - to compute the contribution of the rule to the weight of the conclusion (this is computed from the weight of the rule w and the weight of the condition a),
5. $GLOB(w'_1, w'_2, ..., w'_n)$ - to compose the contributions of more rules with the same conclusion.

Algebraic theory defines a set of axioms, the combination functions must fulfill. Different sets of combination functions can thus be implemented. We call these sets "inference mechanisms". The NEST system uses "standard", "logical" and "neural" one. These mechanisms differ in the definition of the functions CTR and $GLOB$ (the respective formulas are shown in Tab. 2).

Standard inference mechanism is based on "classical" approach of MYCIN and PROSPECTOR expert systems. The contribution of a rule is computed Mycin-like, the combination of contributions of rules with the same conclusion is computed Prospector-like.

Logical inference mechanism is based on an application of the completeness theorem for Lukasiewicz many-valued logic. The task of the inference mechanism is to determine the degree in which each goal logically follows from the set of rules (understood as a fuzzy axiomatic theory) and user's answers during consultation [1]. This degree can be obtained by using the *fuzzy modus ponens* inference rule. To combine contributions of more rules, logical inference mechanism uses the *fuzzy disjunction.*

Neural inference mechanism is based on an analogy with active dynamics of neural networks. To obtain results that correspond to the output of a neuron, the contribution of a rule is computed as a weighted input of the neuron and the global effect of all rules with the same conclusion is computed as piecewise linear transformation of the sum of weighted inputs.

The remaining functions are defined in the same way for all three mechanisms: negation of weight w is evaluated as $-w$, conjunction of weights is evaluated as minimum, and disjunction of weights is evaluated as maximum.

Two different notions of "not known" answer are introduced in NEST. First notion, "irrelevant", is expressed by the weight 0; this weight will prevent a rule having either a proposition or it's negation in conditional part from being applied. Second notion, "unknown", is expressed by the weight interval $[-1, 1]$; this weight interval is interpreted as "any weight". Uncertainty processing has thus been extended to work with intervals of weights. The idea behind is to take into account all values from the interval in parallel. Due to the monotonicity of the combination functions, this can be done by taking into account the boundaries of intervals only.

Table 2. Functions CTR and $GLOB$ for different inference mechanisms

inference mechanism	$CTR(a,w)$ for $a > 0$	$GLOB(w'_1, w'_2, ..., w'_n)$
standard	$a \cdot w$	$\frac{w'_1 + w'_2}{1 + w'_1 \cdot w'_2}$
logical	$sign(w) \cdot \max(0, a + \|w\| - 1)$	$\min(1, \sum_{w'>0} w') - \min(1, \sum_{w'<0} \|w'\|)$
neural	$a \cdot w$	$\min(1, \max(-1, \sum_{i=1}^{n} w'_i))$

2.3 Consultation with the System

Nest offers several modes of consultation. The *dialogue* mode is the classical question/answer mode when the system selects current question using backward chaining. The *questionnaire* mode allows to fill-in answers in advance; the system then directly infers the goals using forward chaining. In *dialogue/questionnaire* mode the user can input some volunteer information (using questionnaire), during further consultation the system asks questions if needed.

In each of this mode, the user answers the questions concerning the input attributes. According to the type of attribute, the user gives the weight (for binary attributes), the value and its weight (for single nominal attributes), list of values and their weights (for multiple nominal attributes), or the value (for numeric attributes). Questions not answered during consultation get the default answer "unknown" [-1,1] or "irrelevant" [0,0], Answers can be postponed – the user can return to them after finishing the consultation. The result of consultation is shown as a list of goals (resp. all propositions) together with their weights.

3 Building the AtherEx System

3.1 Knowledge Acquisition

The knowledge for the AtherEx system was created in a two-step process. At first a machine learning algorithm has been applied to the data from an epidemiological study of atherosclerosis primary prevention, then, the obtained rule set has been revised and refined by the domain expert.

In the early seventies of the twentieth century, a project of extensive epidemiological study of atherosclerosis primary prevention was developed under the name National Preventive Multifactor Study of Hard Attacks and Strokes in the former Czechoslovakia. The aims of the study were:

1. to identify atherosclerosis risk factors prevalence in a population considered to be the most endangered by possible atherosclerosis complications,
2. to follow the development of these risk factors and their impact on the examined men health, especially with respect to atherosclerotic CVD,

KEX algorithm

Initialization

1. forall category (attribute-value pair) A add $A \Rightarrow C$ to $OPEN$
2. add empty rule to the rule set KB

Main loop

while $OPEN$ is not empty do

1. **select** the first implication $Ant \Rightarrow C$ from $OPEN$
2. **test** if this implication significantly improves the set of rules KB build so far (we test using the χ^2 test the difference between the rule validity and the result of classification of an example covered by Ant) then add it as a new rule to KB
3. for all possible categories A
   (a) **expand** the implication $Ant \Rightarrow C$ by adding A to Ant
   (b) **add** $Ant \wedge A \Rightarrow C$ to $OPEN$ so that $OPEN$ remains ordered according to decreasing frequency of the condition of rules
4. **remove** $Ant \Rightarrow C$ from $OPEN$

Fig. 1. Simplified sketch of the KEX rule learning algorithm

3. to study the impact of complex risk factors intervention on their development and cardiovascular morbidity and mortality,
4. 10-12 years into the study, to compare risk factors profile and health of the selected men, who originally did not show any atherosclerosis risk factors with a group of men showing risk factors from the beginning of the study.

The data collected within this study thus concern the twenty years lasting longitudinal study of the risk factors of the atherosclerosis in the population of 1 417 middle aged men [2]. To obtain rules from the data we used the algorithm KEX [2]. This algorithm creates decision rules in the form

$$Ant \Rightarrow C(w),$$

where Ant is a conjunction of attribute-value pairs, C is the class attribute, and w is weight of the rule (from the interval [0,1]). During knowledge acquisition, KEX works in an iterative way, in each iteration testing and expanding an implication $Ant \Rightarrow C$. This process starts with default rule weighted with the relative frequency of the class C and stops after testing all implications created according to the user defined criteria. The induction algorithm inserts only such rules into the knowledge base, for which the validity[3] cannot be inferred from the existing rules. The inference (combination of weights of different rules) is based on the pseudobayesian combination function

$$w_1 \oplus w_2 = \frac{w_1 \cdot w_2}{w_1 \cdot w_2 + (1 - w_1) \cdot (1 - w_2)}.$$

[2] These data have been used for the ECML/PKDD Discovery Challenge workshops - see `http://lisp.vse.cz/challenge` for details.

[3] We compute the validity of a rule from the four-fold contingency table as $P(C|Ant)$.

Table 3. Rule bases created from the STULONG data

Rule base	no.rules	overall accuracy	accuracy for non-risk group	accuracy for other groups
1	19	0.87	0.83	0.88
2	39	0.84	0.74	0.87
3	32	0.77	0.63	0.83
4	27	0.73	0.48	0.83

Let us stress, that this function corresponds to the "standard" *GLOB* function of the system NEST and that the rules created by KEX correspond[4] to the apriori and compositional rules of NEST.

When comparing KEX with divide–and–conquer algorithms (like C4.5) or set covering algorithms (like CN2), we can observe, that:

– KEX creates more rules (because KEX does not remove covered examples),
– the set of rules can obtain both a rule and its sub-rule (the redundancy of rules is evaluated using statistical test),
– examples are assigned to class with uncertainty.

Using KEX we analyzed the data concerning examination of patients when entering the study. These data contain the information about life style, personal history, family history, some laboratory tests and about classification w.r.t atherosclerosis risk (non risk, risky, pathological group). We performed several analyses for different subsets of input attributes:

1. classification based only on already known risk factors (this rule base should confirm the classification of patients in the analyzed data),
2. classification based on attributes concerning life style, personal and family history (but without special laboratory tests),
3. classification based on attributes concerning life style and family history,
4. classification based only on attributes concerning life style.

The classification accuracies (computed using 10 fold cross-validation) of the rule bases resulting from these analyses are summarized in Tab. 3. As a final output from this first (machine learning) step of building the knowledge base, we selected the result of the second type of analyses. The reason for this choice was twofold: the rules have reasonable high classification accuracy and they do not use any "special" attributes concerning laboratory tests.

The set of rules obtained using KEX has been revised by the domain expert who suggested following improvements:

1. add the attribute "total cholesterol" and respective rules,
2. add rules for remaining values of an attribute, if at least one value of this attribute occur in rules obtained from data,

[4] We only have to transform the weights of rules from $[0, 1]$ to $[-1, 1]$.

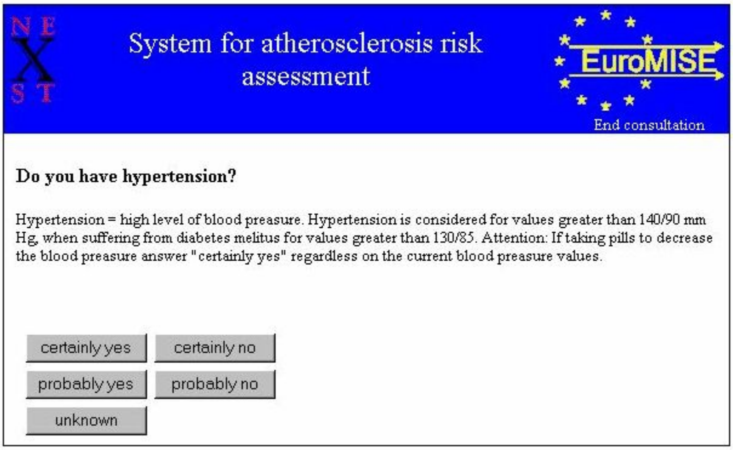

Fig. 2. Screenshot of the system

3. use the goals "no risk", "low risk", "medium risk" and "high risk" instead of original groups taken from data.

3.2 Implementation

We used the client/server version of Nest to implement the AtherEx system. In this version, the server is a web server running under MS Windows and the client is a web browser (like Internet Explorer). Different page layouts can be defined for different knowledge bases. To make AtherEx user-friendly for users who are neither experts in expert systems, nor experts in medicine, we built a front end, that hides the details about inference and uncertainty processing. The system works in dialogue mode, showing one question on a single page. The questions (their number is 22) are grouped into following groups:

- questions concerning personal data (marital status, education, BMI, cholesterol),
- questions concerning life style (smoking, physical activity in job and after job, consumption of alcohol, coffee or tea),
- questions concerning personal history (hypertension, myocardial infarction, diabetes),
- questions concerning family history (hypertension, myocardial infarction, diabetes, angina pectoris or ictus for parents).

The user can answer the questions using predefined values (buttons) "certainly yes", "probably yes", "probably no", "certainly no", or "unknown" (Fig. 2 shows the question about hypertension).

4 Conclusions

The AtherEx expert system described in the paper should help non-expert users to determine their atherosclerosis risk. We see the main advantages of our system (when compared with the CVD risk calculators) in its ability to infer a conclusion from incomplete and/or uncertain input information (the user need not to answer all questions). Our experiments with the machine learning algorithm KEX (see Tab. 3) have shown that the information about life style can be used instead of laboratory tests, that are usually not available for this type of users. AtherEx is now tested by domain expert and other physicians from the EuroMISE center in Prague (http://www.euromise.cz) with similar results. Anyway, the resulting classification does not substitute a diagnosis done by a specialist, it is rather a recommendation that should by consulted with a physician.

AtherEx is available for on-line consultations at http://146.102.170.51. The current version does not consider changes over time. In our future work we plan to include knowledge dealing with the dynamics of the risk factors. As the rules are based on data concerning middle-aged man, we also plan to investigate the applicability of AtherEx to the whole population.

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