

Patient-Specific Adaptation of Medical Knowledge in an Extended Diagnostic and Therapeutic Consultation System

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ABSTRACT: CADIAG-IV is a medical consultation system for internal medicine that uses the concepts of fuzzy sets, fuzzy numbers, and fuzzy logic to deal with uncertainties inherent in medical knowledge. Associations between medical entities are represented as rules and defined by various relationships. Reasoning is based on an iterative application of the compositional rule of fuzzy inference. Since large parts of medical knowledge interact and therefore the inferred diagnoses are usually influenced by the state and medication of the respective patient, CADIAG-IV applies two concepts to handle these dependencies. First, the application of fuzzy sets in the transformation from observational data to abstract symptoms, signs, and test results is sensitive to certain aspects of the state of the patient. Second, the rules in the knowledge base may be dynamically enabled, altered, or disabled in response to particular characteristics of a patient. This paper discusses CADIAG-IV and its concepts of patient-specific adaptation.

KEYWORDS: consultation system, fuzzy logic, patient-specific adaptation, data-to-symbol conversion, meta-rules

INTRODUCTION

Most of the given medical knowledge on symptoms (a collective term used to denote symptoms, signs, and test results), diseases, and therapies and on the causal and statistical relationships between them is intrinsically uncertain (measurements are imprecise, linguistic categories are characterized by vague or fuzzy borderlines, the co-occurrence of symptoms and diseases is stochastically uncertain, and medical data and knowledge are often incomplete). As a consequence, most of the developed medical consultation systems, which process patient data by applying this uncertain knowledge, use different methods to deal with uncertainty. Prominent methods are the probability theory, the fuzzy set theory, and the possibility theory. In addition, a rather large portion of medical knowledge depends on contextual influences such as specific aspects of the physical state of or the medication prescribed to the patient. Failing to take these influences into consideration may falsify or even invalidate a diagnosis.

CADIAG-II [1],[2]—the basic concepts of CADIAG-II were published in 1980 [3]—, CADIAG-III [4], and their successor CADIAG-IV (CADIAG stands for Computer Assisted Diagnosis) are data-driven diagnostic and therapeutic consultation systems that do not only consider uncertainty inherent in medical knowledge but also implement concepts for patient-specific adaptation of medical knowledge in order to optimally adapt the applied medical knowledge to the individual patient. They provide diagnostic hypotheses, explanations for them, and proposals for useful examinations in response to the input of symptoms, signs, and test results obtained for a patient. To deal with uncertainties in medical terminology and medical relationships, they rely on the theory of fuzzy sets, particularly on the concepts of linguistic variables and fuzzy logic [5],[6].

After an introduction into the basics of knowledge representation, the ways of dealing with uncertainty, and inference in CADIAG-IV, a detailed overview of the principles of patient-specific adaptation used in CADIAG-IV will be given.

METHODS

CADIAG-IV

In CADIAG-IV, medical knowledge is represented in the form of rules containing definitional, causal, statistical, or heuristic relationships between single or compound antecedents and consequences [3],[7],[8],[9]. Rules with a single medical entity as antecedent (i.e., a symptom, disease, or therapy) express associations or correlations between two medical entities. Compound antecedents are represented as symptom combinations, which are combinations of medical entities connected by *and*, *or*, and *not* as well as the operators *at least* and *at most*. They allow both the definition of pathophysiological states and the incorporation of very specific, complex criteria for diagnosing diseases. The associations are characterized by three relationships: first, the basic kind of correlation between the antecedent and the consequence of the rule, i.e., whether the antecedent and consequence of the rule are positively or negatively correlated (or neutral); second, the frequency of occurrence of the antecedent with the consequence (for positively correlated entities) and of the antecedent with not-the-consequence (for negatively correlated entities); and third, the strength of confirmation or exclusion of the antecedent for the consequence.

Thus, rules are interpreted as a set of binary relationships between antecedents and consequences. The strength of either of the last two relationships is expressed by a fuzzy number, which is a normal fuzzy set in the interval $[0, 1]$ whose support is bounded and whose α -cuts are closed intervals for every $\alpha \in (0, 1]$. CADIAG-IV currently supports Singletons as well as Lambda and PI shapes. Figure 3 depicts a fuzzy number representing a value of about 0.8 in a PI shape. Table I presents the syntax of CADIAG-IV rules in extended Backus-Naur Form (eBNF).

<code><Rule></code>	<code>::=</code>	<code><Symptom> :- <Symptom> ,<SOC>, <FOO>, {+ -}</code> <code> <Disease> :- <Symptom> ,<SOC>, <FOO>, {+ -}</code> <code> <Disease> :- <Disease> ,<SOC>, <FOO>, {+ -}</code> <code> <Disease> :- <SYC-Name> ,<SOC>, <FOO>, {+ -}</code> <code> <Therapy> :- <Disease> ,<SOC>, <FOO>, {+ -}</code> <code> <Therapy> :- <Therapy> ,<SOC>, <FOO>, {+ -}</code> <code> <Symptom> :- <Disease> ,<SOC>, <FOO>, {+ -}</code> <code> <Symptom> :- <Therapy> ,<SOC>, <FOO>, {+ -}</code> <code> <Disease> :- <Therapy> ,<SOC>, <FOO>, {+ -}</code>
<code><Symptom-Combination></code>	<code>::=</code>	<code><SYC-Name> := <SYC-Expression></code>
<code><SYC-Expression></code>	<code>::=</code>	<code><SYC-Term> {v <SYC-Term>}*</code>
<code><SYC-Term></code>	<code>::=</code>	<code><SYC-Factor> {^ <SYC-Factor>}*</code>
<code><SYC-Factor></code>	<code>::=</code>	<code>[~] <SYC-Variable></code>
<code><SYC-Variable></code>	<code>::=</code>	<code><Symptom></code> <code> <Disease></code> <code> <Therapy></code> <code> <IC-Name></code> <code> (<SYC-Expression>)</code> <code> <SYC-MIMA-Term></code>
<code><SYC-MIMA-Term></code>	<code>::=</code>	<code>{fzatleast fzatmost}(<Part-Whole>, <SYC-Variable-List>)</code>
<code><SYC-Variable-List></code>	<code>::=</code>	<code><SYC-Expression> {, <SYC-Expression>}*</code>
<code><SOC></code>	<code>::=</code>	<code><Fuzzy-Degree></code>
<code><FOO></code>	<code>::=</code>	<code><Fuzzy-Degree></code>
<code><Symptom></code>	<code>::=</code>	<code>S<Integer></code>
<code><Disease></code>	<code>::=</code>	<code>D<Integer></code>
<code><Therapy></code>	<code>::=</code>	<code>T<Integer></code>
<code><SYC-Name></code>	<code>::=</code>	<code>SYC<Integer></code>
<code><IC-Name></code>	<code>::=</code>	<code>IC<Integer></code>
<code><Fuzzy-Degree></code>	<code>::=</code>	<code>PI (<Degree>, <Degree>, <Degree>, <Degree>)</code> <code> Lambda (<Degree>, <Degree>, <Degree>)</code> <code> Singleton (<Degree>)</code>
<code><PartWhole></code>	<code>::=</code>	<code><Integer>/<Integer></code>
<code><Degree></code>	<code>::=</code>	<code>0.{<Digit>}+ 1.0</code>
<code><Integer></code>	<code>::=</code>	<code>{<Digit>}+</code>
<code><Digit></code>	<code>::=</code>	<code>0 1 2 3 4 5 6 7 8 9</code>

Table I: The syntax of CADIAG-IV rules in eBNF

A typical rule of CADIAG-IV according to the syntax depicted above is given in the form:

```
D77 :- SYC7, Singleton (1.0), Singleton (1.0), +
SYC7 :- (D1 ^ S602) ^ ¬ ( (S1001 v S758) v S761)
```

where D77 is ‘Seropositive Chronic Polyarthritis, Stadium I’, D1 is ‘Rheumatoid Arthritis’, S602 is ‘Waller-Rose-Test, Positive’, S1001 is ‘X-Ray, Joints, Symptoms of Arthritis, Erosions’, S758 is ‘X-Ray, Joints, Subluxation’, and S761 is ‘X-Ray, Joints, Ankylosis of the Peripheral Joints’.

This rule is interpreted as

```
IF      Rheumatoid arthritis AND Waller-Rose test, positive AND
        NOT (
            x-ray, joints, symptoms of arthritis, erosions OR
            x-ray, joints, subluxation OR
            x-ray, joints, ankylosis of the peripheral joints
        )
THEN   seropositive chronic polyarthritis, stage I
```

and the left-hand side of the rule confirms the right-hand side while the left-hand side obligatory occurs with the present right-hand side of the rule.

The overall process of deriving particular diagnoses from a given set of personal and medical data about a patient consists of four steps in CADIAG-IV [1] and is depicted in the diagram in Figure 1.

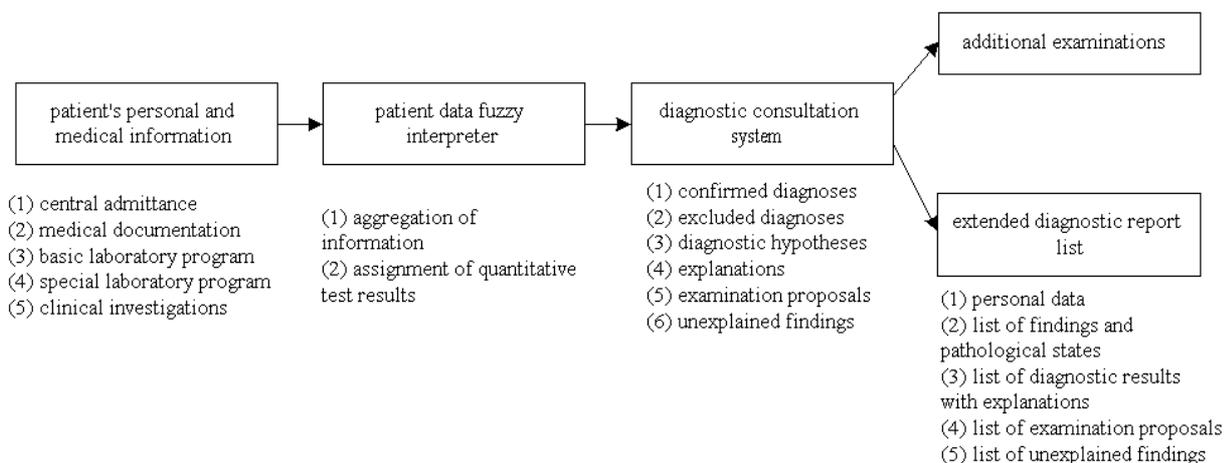


Figure 1: The consultation process in CADIAG-IV

The physician starts the consultation process by entering personal and medical data about the patient. This information usually represents patient data on a detailed observational level, i.e., detailed history items, signs from physical examinations, quantitative laboratory test results, or the outcome of certain clinical investigations. CADIAG-IV establishes a clear distinction between information on this observational level and abstract symptoms commonly used in diagnostic discourse. Therefore, in the beginning of a consultation, a transformation step known as data-to-symbol conversion, which aggregates and abstracts medical information provided by the physician into this internal representation, is applied [10].

The data-to-symbol conversion assigns two values to every medical entity: (1) the strength of evidence and (2) the strength of counterevidence. Both values are—in order to overcome the criticism of rather sharp and therefore not very fuzzy point values in CADIAG-II—fuzzy numbers in [0, 1]. The interpretation of these values is as follows: a fuzzy number representing zero means that we have no evidence (or counterevidence) regarding this medical entity, while a fuzzy number representing unity is interpreted as proof (or exclusion). Intermediate values denote evidence that is not sufficient to prove or exclude the entity in question. A value v is assigned to medical entities that were not examined.

The mechanism of aggregation in data-to-symbol conversion combines one or more documentation items into a simplified binary symptom. For this purpose, the Boolean logical combination of detailed original observations connected by *and*, *or*, and *not* as well as the operators *at least* and *at most* is evaluated into a value representing the strength of evidence of the aggregated symptom.

The concept of abstraction is used to transform quantitative test results into abstract symptoms and to assign the strength of confirmation to them. One example of an abstracted symptom is *elevated glucose serum level*, which is set according to the quantitative result of the glucose test and the definition of *elevated*. The formal modeling of semantic medical concepts such as *elevated* that considers their inherent uncertainty, visible in their gradual transition to adjacent medical concepts, is based on fuzzy set theory. Fuzzy sets are defined by membership functions, which assign to every symptom S_i a degree of membership μ . These degrees are real numbers and express the degree of compatibility of the measured concrete value with the semantic concepts under consideration. They range from zero to unity, where zero means 'Not compatible' and unity 'Fully compatible'. CADIAG-IV allows both to use type-1 membership functions and transforms the computed degree of compatibility to a fuzzy number either as Singleton or in a PI shape to be used as evidence of the particular abstracted symptom. For example, the value of 0.8 computed as the degree of compatibility to the concept *normal glucose serum level* as shown in Figure 2 is transformed to the evidence value depicted in Figure 3.

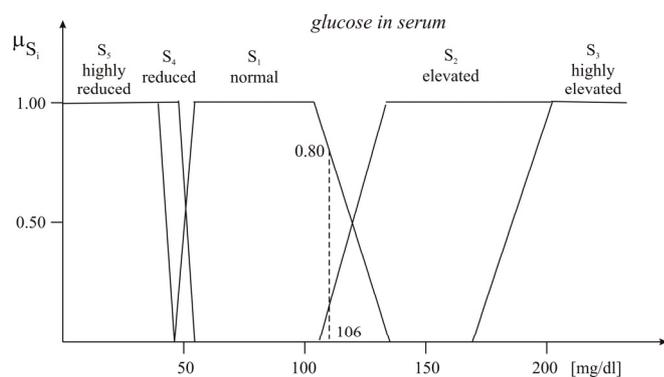


Figure 2: Symbolic representation of medical entities using fuzzy sets

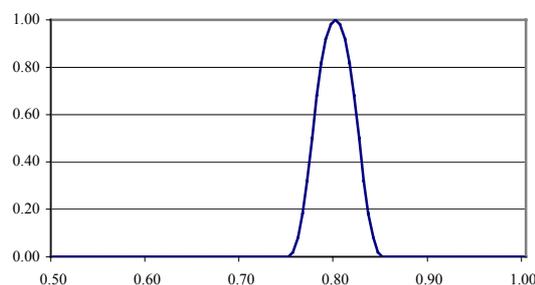


Figure 3: Fuzzy number representing a value of about 0.8

Starting with the set of medical entities and the corresponding values for evidence and counterevidence generated by the data-to-symbol conversion, CADIAG-IV infers sets of confirmed diagnoses, excluded diagnoses, diagnostic hypotheses, and unexplained findings. The basic concept on which the inference mechanism relies is the compositional rule of fuzzy inference [11], which allows inference under uncertainty. The rules contained in the knowledge base are iteratively applied to the set of medical entities applying to the patient until a fix point is reached. In addition to the diagnostic result, CADIAG-IV proposes a list of useful examinations, which probably will confirm or exclude some of the generated diagnostic hypotheses. An explanation of the generated solution is also provided.

Since a deeper insight into the inference mechanism is not required for the purpose of this paper, the reader is referred to publications [1],[2],[7],[12], and [13] for further details.

REASONS FOR PATIENT-SPECIFIC ADAPTATION IN CADIAG-IV

As mentioned above, most of the given medical knowledge on medical entities and the relationships between them is uncertain. The previously described knowledge representation and inference mechanism uses various concepts to deal with uncertainty:

- (1) The definition of semantic medical concepts such as *elevated* is inherently uncertain. Therefore, it is not possible to specify crisp intervals in the value space of quantitative test results to derive abstracted symptoms from. CADIAG-IV uses type-1 fuzzy sets to model semantic medical concepts, since they are capable of considering the inherent uncertainty in the form of gradual transitions to adjacent medical concepts.
- (2) In descriptions of diseases, precise relationships between symptoms and diseases can seldom be found. A typical definition of a disease would be 'acute pancreatitis is almost always connected with sickness'. Thus, neither a definite statement whether a symptom proves or excludes a particular disease, always or never occurs with a

particular disease, nor a single point value like 0.95, for instance, may be specified to describe this relationship, since the interpretation of ‘almost always’ will vary from one physician to another. Therefore, in CADIAG-IV medical associations are described by fuzzy numbers, which allow both to model the uncertainty of associations and the uncertainty in the value describing the strength of the association.

The concepts introduced up to this point are suitable for taking generally applicable uncertainties into account. However, a large part of medical knowledge has to be adapted to characteristics of the patient—including certain aspects of the physical state and medication—and the hospital or laboratory in which the examination has been performed, in order to be applicable or correct. CADIAG-IV uses two concepts to perform this process termed patient-specific adaptation of medical knowledge: the application of fuzzy sets in the transformation from observational data to abstract symptoms is sensitive to the characteristics of the patient and the rules in the knowledge base may be dynamically enabled, altered, or disabled according to the patient’s characteristics.

PATIENT-SPECIFIC APPLICATION OF FUZZY SETS

To support the interpretation of medical information on an observational level that is sensitive to individual patient characteristics, fuzzy membership functions for various contexts can be defined. Currently we have identified five contexts as being necessary in CADIAG-IV:

- (1) the gender of the patient in question (e.g., the blood sedimentation rate depends on the gender),
- (2) the age of the patient in question (e.g., the serum IgE level in children greatly depends on the age),
- (3) the laboratory in which the examination was performed (since there are different implementations of a single examination and the concrete result depends on the applied methodology),
- (4) influences due to another prevailing symptom, disease, prescribed drug or therapy (e.g., in pregnancy a large number of laboratory parameters deviate from those of non-pregnant women), and
- (5) influences due to a combination of symptoms, diseases, therapies, and medications (e.g., the large number of drugs applied to a patient in an intensive care unit influences various laboratory parameters).

<BoolMedData>	::=	S{03 04 05}_<Integer>
<NumMedData>	::=	S{03 04 05}_<Integer>
<ComparisonOperator>	::=	= < < <= > >=
<ContextExpression>	::=	<ContextTerm> {∨ <ContextTerm>}*
<ContextTerm>	::=	<ContextFactor> {∧ <ContextFactor>}*
<ContextFactor>	::=	<Comparison> <BoolMedData> <Symptom> <Disease> <Therapy>
<Comparison>	::=	<NumMedData> <ComparisonOperator> <Integer>

Table II: The syntax of expressions for specifying contexts in eBNF

A context can be formalized as a logical combination of medical data items (i.e., patient information on an observational level) and medical entities as specified in Table II.

Depending on the particular characteristics of the patient in question, specific contexts are taken into account when converting the quantitative test result to the corresponding semantic medical concept. For this purpose, for every context, first the degree of compatibility of the patient to a particular semantic medical concept is calculated. Second, the maximum of these values is calculated as the degree of compatibility of the patient to the semantic medical concept [10]. It can be shown that there are various fields of application, especially in the interpretation of laboratory test results, where this procedure improves the resulting interpretation or even is necessary for a correct interpretation.

ADAPTATION OF RULES IN THE KNOWLEDGE BASE

The application of all rules in the knowledge base in every inference cycle consumes a vast amount of computing power. In many cases, though, a lot of rules will not contribute to the result of the consultation since the antecedent evaluates to false due to the symptoms found in the patient under consideration. Nevertheless the precondition is evaluated in every inference cycle again and, therefore, slows down the entire system. For example, there may be rules in the knowledge base that require the patient to be pregnant so that the consequence of the rule may be inferred. Thus,

the patient, of course, has to be female. Since it is not necessary to evaluate this condition in the case of a male patient for all rules including this precondition in every inference cycle, a better solution would be a dynamic exclusion, alteration, and inclusion of rules of this kind during the inference process.

For this purpose the notion of meta-rules has been introduced into the definition of CADIAG-IV rules. A meta-rule does not produce any diagnostic results but only has effects on the knowledge base itself by enabling, altering, or disabling a particular rule. The definition of a meta-rule is shown in Table III.

<Rule>	::=	...
		<Rule-Modifier> :- <SYC-Name>, <Borderline>
		<Rule-Modifier> :- <Symptom>, <Borderline>
		<Rule-Modifier> :- <Disease>, <Borderline>
		<Rule-Modifier> :- <Therapy>, <Borderline>
<Rule-Modifier>		SetActive(<Internal-RuleID>),
		SetInactive(<Internal-RuleID>)
<Borderline>	::=	<Fuzzy-Degree>

Table III: The syntax of meta-rules in eBNF

The rule to be enabled, altered, or disabled is referenced by an internal ID being available for every rule. Since the activation, alteration, and deactivation of rules may have a deep impact on the diagnostic result, the knowledge engineer is required to specify a borderline value the degree of compatibility of the antecedent has to exceed so that the meta-rule is executed.

While the application of this concept primarily has positive effects on the runtime behavior of the consultation system—the diagnostic result would not differ without application of this mechanism—a further potential use of this concept is conceivable. If the relationships (i.e., the frequency of occurrence and the strength of confirmation) of a particular association depend on any context, the knowledge engineer could create a single rule for every context and alternately enable, alter or disable the particular rules.

RESULTS

The biggest part of knowledge representation and inference formalism and the concept of context-sensitive data interpretation according to gender, age, and the laboratory of origin have already been applied and evaluated in CADIAG-II, where they have significantly contributed to the success of the system [1],[2],[3],[7]. In the following we will deal with the implementation of the concepts of patient-specific adaptation in CADIAG-IV in more detail.

CADIAG-IV is embedded into MedFrame, a medical expert system shell currently being implemented at the Section on Medical Expert and Knowledge-Based Systems of the Department of Medical Computer Sciences in the University of Vienna Medical School [14]. MedFrame streamlines the implementation of modern expert systems by providing a set of powerful tools and concepts. Beside a lot of tools for developing client/server- and Internet-based consultation components and attractive user interfaces, MedFrame offers the following set of concepts the implementation of CADIAG-IV is based on:

- an object model for storing domain knowledge using various representation formalisms [15],
- a set of classes for storing patient administrative and examination data [15],
- a set of classes based on the theory of fuzzy sets [5],[6] to support the modeling of uncertainties and to consider uncertain facts in inference including: a large set of type-1 membership functions (e.g., PI shapes, Gamma shapes, ...) [16], the implementation of the concept of type-1 fuzzy sets, and the implementation of fuzzy numbers and tools for calculating with them.

In fact, everything required for patient-specific adaptation is available in MedFrame. While CADIAG-IV is currently in the process of being developed, the parts of MedFrame needed for the purpose of patient-specific adaptation have been completed and will be examined in the following.

Figure 4 depicts the model of the classes involved in patient-specific adaptation in CADIAG-IV in Unified Modeling Language (UML) notation. Medical knowledge is stored in objects of the classes *MedicalDataDef* (which describe medical knowledge on the observational level) as well as *MedicalEntityDef* (representing medical knowledge on the abstracted level) and its subclasses. CADIAG-IV rules are implemented in terms of instances of the class *Tuple*.

Concrete patient information on the observational level is stored in instances of class *MedicalData* while the aggregated and abstracted symptoms, diseases, and therapies can be found in instances of class *MedicalEntity*.

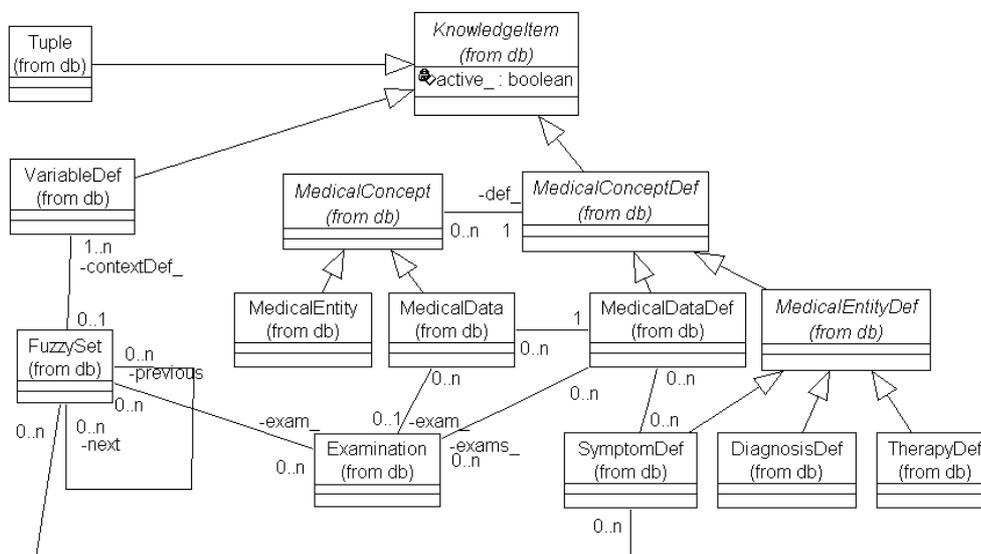


Figure 4: The classes involved in patient-specific adaptation in UML notation

Patient-specific application of fuzzy sets is realized in the following manner: the instances of class *FuzzySet* determine the shape and positioning of the various fuzzy sets, the definition of the corresponding contexts is realized as instances of class *VariableDef*, which contain fuzzy logical expressions as defined in Table II. The medical data item a particular fuzzy set belongs to is stored in the connection from *FuzzySet* via *Examination* to *MedicalDataDef*. This connection assigns a particular fuzzy set to a medical data item gained with the specified examination. Thus, while the information on how gender, age, and interacting symptoms, diseases, and therapies influence data-to-symbol conversion are stored in instances of *VariableDef*, the adaptation information due to laboratory peculiarities is realized in the connection via the *Examination* class.

The dynamic activation, alteration, and deactivation of rules have been realized in a straightforward manner. Every rule (i.e., an instance of *Tuple*) inherits an attribute *active_* from its superclass *KnowledgeItem*. This attribute indicates whether the corresponding item of the knowledge base shall be included in the inference process. Thus, before starting a new inference cycle, all meta-rules are evaluated by the inference engine and, if necessary, particular rules are enabled, altered, or disabled according to the characteristics of the patient under consideration.

CONCLUSION

The applicability of context-sensitive data interpretation according to gender, age, and the laboratory from which the medical data originate, was previously shown in CADIAG-II. The expansion of this concept to any interacting symptoms, diseases, or therapies in CADIAG-IV will further improve the quality of CADIAG's inference mechanism.

In addition, the concept of patient-specific adaptation of the rules in the knowledge base will significantly increase the performance of CADIAG-IV. We also plan to extend this concept from just dynamically enabling, altering, and disabling rules to setting any attribute of rules in the knowledge base at runtime. Thus, the knowledge engineer could create meta-rules that adapt, for example, the strength of confirmation of a particular rule according to a given characteristic of the patient under consideration.

Relying on the concepts introduced in CADIAG-II, on the rather advanced implementation of the medical expert system shell MedFrame, and on previously implemented parts of patient-specific adaptation and the inference mechanism of CADIAG-IV, the first working prototype of CADIAG-IV is scheduled for the beginning of next year.

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