11 APPROXIMATE REASONING IN COMPUTER-AIDED MEDICAL DECISION SYSTEMS

Jean-Christophe BUISSON

Abstract:

A survey on existing knowledge-based medical systems using approximate reasoning is presented. It is shown that the medical goals at which such systems aim at must be carrefully designed, in order to be accepted by the medical community, and that taking into account imprecision and uncertainty in facts and knowledge is a major ingredient for success. This survey shows a large diversity of knowlege representation and reasoning models. Particular medical and mathematical pitfalls are pointed out, among them the problem of representing directly symptoms and diseases with fuzzy sets, which leads to interpretation problems. It is shown that possibility distributions are a good means to express most medical notions. Following the tradition of MYCIN, most systems represent and propagate uncertainty, whereas imprecision is rarely dealt with when it should.

11.1 INTRODUCTION

The expert systems trend created by MYCIN [43] provoqued a great interest in the medical community at the beginning of the 80's. A large number of projects were started, which were more or less aimed at modelling the diagnostic process of the different medical specialities, very often without considering the medical suitability of their approach.

At the end of the 80's, the expert system approach met with renewed criticism because of its inability to provide robust decision models which accurately represent real-world situations [36]. Most medical projects were abandoned, because of their poor intrinsic results as well as their inability to be integrated into a therapeutic process. Typically, the systems which were doing medical diagnoses from data interactively provided were doomed to a failure, when they were used in situations where real (and better) physicians were at hand [32]. As for systems which were to be used in remote places (boats, etc.), they were faced with the difficult problem of facts elicitation from the user (which is an expert task in itself in medicine).

Most systems presented here have been around for years, and are or have been used routinely in real therapeutic situations. They bypassed the upmentionned difficulties by being a useful part of an organized medical process. Tey are taking into account the inherent imprecision and uncertainty of medical facts and laws, and therefore the robustness of their results is another important aspect of their success.

11.2 CRITICAL SURVEY OF SIGNIFICANT SYSTEMS

11.2.1 MYCIN, the pioneer

MYCIN is the first rule-based medical expert system ever created. It's been developed mainly between 1972 and 1978 at the Heuristic Programming Project of Stanford University [15]. It's an old system, no longer used, but its influence on contemporary programs is still visible. Its approximate reasoning model suffered many inconsistencies, but it dealt with the key problems of approximate reasoning, namely uncertainty representation and propagation, conflicts resolution, facts elicitation and knowledge acquisition.

MYCIN gives advice on blood infectious diseases. At the time, surveys showed that a large part of patients who required antimicribial therapy were given a drug that was inappropriate for their clinical condition. An improved therapy selection in patients requiring therapy is precisely the decision task with which MYCIN is designed to assist.

MYCIN works in four steps:

1. decide whether the patient has a significant infection
2. determine the likely identity of the offending organism
3. decide what drugs are apt to be effective against this organism
4. choose the drug that is most appropriate given the patient's clinical conditions

11.2.1.1 Facts representation. Through a specific vocabulary (clinical parameters in contexts), facts in MYCIN represent variable values on finite domains. A fact 'the patient is a child', as expressed verbally by the interaction modules of MYCIN, tells with certainty that the age of the patient has the value 'child', among the three of the domain {'child', 'teenager', adult'}. It must be noted these values correspond to the crisp intervals $[0, 13]$, $(13, 20]$ and $(20, 150]$

respectively. In fact, the domain of a clinical parameter is always a finite set of values, and continuous domains such as age are cut into mutually exclusive parts.

MYCIN associates to each value *val* of a clinical parameter p a certainty factor $CF \in [0,1]$, with the following meaning:

- $CF = +1$: MYCIN is certain that *val* is the value of p
- $CF = -1$: MYCIN is certain that *val* is not the value of p
- $CF = c(c > 0)$: MYCIN estimates with the degree c that *val* is the value of p
- $CF = c(c < 0)$: MYCIN estimates with the degree c that *val* is not the value of p
- $CF = 0$: MYCIN does not have any idea about *val* being the value of p (initial state)

So the certainty of a fact (p, val) can be expressed, not only with true/false, but on a continuous scale. It is easy to express ignorance about a fact by using the certainty degree 0. But it is not possible to represent facts such as 'the patient is about 15 years old', since each domain is already partitionned into a finite number of predefined subdomains.

The certainty factor CF is the difference between two belief measures:

- MB $\in [0,1]$: measure of belief in the hypothesis that *val* is the value of p
- MD $\in [0,1]$: measure of disbelief in the hypothesis that *val* is the value of p
- min(MB,MD) = 0
- CF = MB - MD
- MB(p) = MD($\neg p$) in the binary case $\{p, \neg p\}$

For single-valued clinical parameters, as soon as one of the possible values is declared as certain (CF = +1), all other values are stored with CF = -1.

11.2.1.2 Rules representation and firing. Rules in MYCIN are of the form if premise then action, where an action may be of the form 'the value of the clinical parameter p is *val*, with the certainty c' where $c \in [-1, +1]$ represents an attenuation coefficient of the conclusion. On the 850 conclusion of the 440 rules of MYCIN in 1978, only 160 had an attenuation coefficient equals to +1 or -1.

Conjunctions (resp. disjunction) of conditions are evaluated as the minimum (resp. maximum) evaluation of each condition. Elementary conditions may have many forms, such as:

- KNOWN p: 1 if $CF_{max} > 0.2$, 0 otherwise
- NOTKNOWN p: 1 if $CF_{max} \leq 0.2$, 0 otherwise
- DEFINITE p: 1 if $CF_{max} = 1$, 0 otherwise
- ...

, where CF_{max} is the greatest certainty factor for each possible value of the clinical parameter p. A very important discontinuity is necessarily observed when the input data certainty changes gradually around the arbitrary threshold 0.2.

A rule is fired when the certainty CF_c of its condition part is found greater than the arbitrary threshold value 0.2. For each rule conclusion 'p is *val* with the certainty CF_r', MYCIN computes $CF = CF_c * CF_r$, which will assess the degree of certainty of the conclusion.

If two rules are candidates for firing, and lead to two certainty factors CF_1 and CF_2 for the same conclusion 'p is *val*', the aggregated certainty factor is:

- if $CF_1 * CF_2 \geq 0$ (rules not conflicting): $CF = CF_1 + CF_2 - CF_1 * CF_2$
- if $CF_1 * CF_2 < 0$ (rules conflicting): $CF = CF_1 + CF_2$

These ad-hoc formulas have been very much discussed afterwards. The conflicting case has been improved in 1979 by Van Melle [51]:

$$CF = \frac{CF_1 + CF_2}{1 + \min(|CF_1|, |CF_2|)} \tag{11.1}$$

It can be shown [27] that if (11.1) is used on a binary set $\{u, \overline{u}\}$, it becomes the possibilistic rule of combination with the product, which is associative [27]:

$$\frac{\pi_1(t)\pi_2(t)}{\max_t \pi_1(t)\pi_2(t)} \tag{11.2}$$

where $\pi_i(u) = 1 - MB(\overline{u})$ and $\pi_i(\overline{u}) = 1$ if $MB(\overline{u}) > 0$

The blind combination mechanism may lead to indesirable conclusion, especially if rules having different levels of specificity are used in parallel (as in the example 'if p then q with CF=c' and 'if p and r then not q CF=c").

However, the main problems of certainty propagation as well as combination of conflicting and unconflicting information were correctly stated.

11.2.2 CADIAG-2: general internal medicine

11.2.2.1 Clinical issues. The central goal of the CADIAG-2 project [4] is the development of a medical consultation system for general internal medicine. Its clinical issues are to assist a physician in the differential diagnostic process, by indicating all possible diseases which might be the cause of the patient's pathological symptoms, by proposing useful further examinations to confirm or exclude diagnostic hypotheses, and by indicating all the patient's symptoms not yet accounted for by the system's diagnoses. Its knowledge base is focused mainly on rheumatic and gastroenterological diseases, currently covering about 185 and 110 diseases, respectively, with a special emphasis on rare diseases (an other aspect of its usefulness). An evaluation of CADIAG-2 on 154 patients with rheumatoid arthritis gave an accuracy rate of 88.7% [5].

The elicitation of data is greatly facilitated by the integration of CADIAG-2 into the medical information system of the Vienna General Hospital [3]. This integration allows the collection of the patient's findings for CADIAG-2 via the routine medical documentation and laboratory databases. In addition, patient data not routinely collected can be added to CADIAG-2 through a man-machine interface which processes medical terms given in natural language.

11.2.2.2 The concept of entity and its representation in CADIAG-2. CADIAG-2 deals with the following medical entities:

- the patients, noted P_q, whose set is: $\Pi = \{P_1, ..., P_r\}$
- the symptoms, noted S_i, the set of which is: $\Sigma = \{S_1, ..., S_m\}$
- the diseases, noted D_j, of the set: $\Delta = \{D_1, ..., D_n\}$
- the symptoms combinations primary, noted SCP_k, which are logical combinations (with 'and', 'or', and 'not') of S_i and D_j
- the symptoms combinations secondary, noted SCS_l, logical combinations of SCP_k

Relatively to a patient P_q, each entity ξ_i (symptom, disease, etc.) is considered as a fuzzy subset. ξ_i corresponds to the patient P_q, not in a yes or no way, but with graduality. The value μ_{ξ_i}, between 0 and 1, expresses the degree at which ξ_i is present for the patient P_q, where 0 denotes a complete absence and 1 a complete presence. CADIAG-2 considers this degree also as a particular value of a fuzzy relation, noted $R_{P\xi}$, between the set of patients Π and the set of the considered entities. For instance R_{PS} is the fuzzy relation on $\Pi \times \Sigma$ between the patients (P) and the possible symptoms (S), and a given symptom S_i is present for a given patient P_q with the degree $\mu_{R_{PS}}(P_q, S_i)$ (abbreviated into $\mu_{S_i} \in [0, 1]$).

Finally, $\mu_{\xi_i} =?$ denotes a complete lack of knowledge about the presence or absence of ξ_i for the patient (initial value). This value '?' is ad-hoc, and cannot be any value of $[0, 1]$. Actually, there is no easy way to represent ignorance with this formalism. We'll see later that representing ignorance is a special case of the more general problem of representing disjunctions, and that possibility distributions allow this in a straightforward manner.

When acquiring a new fact, either from the patient data base or interactively from the user, a fuzzy interpreter translates it into membership degrees for the associated entities. It should be noted that a value such as a laboratory result is taken and considered as certain and precisely known.

Most other symptoms are of a yes/no kind. An example of a patient's symptoms pattern given in [1] is:

symptoms	measured or present	fuzzy value $\mu_p(S_i)$
fever	37.5 Celcius Degrees	1.00
elevated fever	idem	0.60
hydrops of the knee	yes	1.00
carditis	yes	1.00
joint pain	yes	1.00
erythema	yes	1.00
previous tonsillitis	yes	1.00
synovial fluid		
staphylococci	?	none
AST elevated	yes	1.00

'fever' and 'elevated fever' are connected to the same measured value of temperature (37.5). This value has been converted by the fuzzy interpreter into the two membership values 1.00 and 0.60. All other symptoms take their value in the domain yes/no, and we can see for 'synovial fluid exam. staphylococci' the ad-hoc value '?' to represent ignorance, with no associated membership value.

11.2.2.3 The problem of representing medical entities with fuzzy sets. 'fever' and 'elevated fever' are called 'symptoms' by Adlassnig. Actually the symptom is 'body temperature = 37.5', and fever' plays the role of a 'pattern', or a 'fuzzy condition'. With only the membership value 0.60 for 'elevated fever' for instance, we know that the information on temperature corresponds only partially to the fuzzy subset 'elevated fever', without knowing why. We cannot guess whether the input information was precise but uncertain, or imprecise/fuzzy and certain.

This problem is mainly due to the fact that the knowledge about the patient's temperature is:

1. only represented by membership degrees w.r.t. fixed fuzzy categories
2. splitted into separated entities (fever and elevated fever for the temperature)

11.2.2.4 The inference process in CADIAG-2. Inference knowledge in CADIAG-2 is expressed by means of fuzzy relation between two entities: relations S_i/D_j and SC_k/D_j for asserting or invalidating diagnoses, relations S_i/S_j and D_i/D_j for handling co-occuring diseases and controling the consistency. A relation between a symptom S_i and a diagnosis D_j for example, is represented with two fuzzy relations:

- the occurence of S_i in case of D_j, noted $R^o_{S_i D_j}$

- the confirmability of S_i for D_j, noted $R^c_{S_i D_j}$

For instance, [1] gives the documented relations between two rheumatic diseases and the symptoms presented in 11.2.2.2:

	symptoms	D1: rheumatic fever		D2: infectious arthritis	
		$\mu_o(S_i, D_1)$	$\mu_c(S_i, D_1)$	$\mu_o(S_i, D_2)$	$\mu_c(S_i, D_2)$
S1:	fever	often		very often	
S2:	elevated fever	often		very often	
S3:	hydrops of the knee	seldom		seldom	
S4:	carditis	very often	often	almost never	
S5:	joint pain	almost always		almost always	
S6:	erythema	often		very seldom	
S7:	previous tonsillitis	very often		very seldom	
S8:	synovial fluid staphylococci	never	never	always	always
S9:	AST elevated	almost always		seldom	

To each qualifier is associated a number which represents it. For instance, to 'very often' is associated the range 64-90, the mean value of it being 77.

So, for the relation between S_4 and D_1, we have:

$\mu_{R^o_{SD}}(S_4, D_1) = 0.77$,
$\mu_{R^c_{SD}}(S_4, D_1) = 0.64$.

Then CADIAG-2 computes four quantities:

1. the occurence indication of D_j for the patient P_q:

$$\mu_{R^1_{PD}}(P_q, D_j) = \max_{S_i} min(\mu_{R_{PS}}(P_q, S_i), \mu_{R^o_{SD}}(S_i, D_j)) \qquad (11.3)$$

This formula as the next three is calculated by means of fuzzy relations compositions (see, e.g., [24]):

$$\mu_{R_{XY}}(u, w) = \sup_{v \in Y} min(\mu_{R_{XY}}(u, v), \mu_{R_{YZ}}(v, w))$$

2. the confirmability indication of D_j for the patient P_q:

$$\mu_{R^2_{PD}}(P_q, D_j) = \max_{S_i} min(\mu_{R_{PS}}(P_q, S_i), \mu_{R^c_{SD}}(S_i, D_j)) \qquad (11.4)$$

3. the non-occurence indication of D_j for the patient P_q:

$$\mu_{R^3_{PD}}(P_q, D_j) = \max_{S_i} min(\mu_{R_{PS}}(P_q, S_i), 1 - \mu_{R^o_{SD}}(S_i, D_j)) \qquad (11.5)$$

4. the non-symptom indication of D_j for the patient P_q:

$$\mu_{R^4_{PD}}(P_q, D_j) = \max_{S_i} min(1 - \mu_{R_{PS}}(P_q, S_i), \mu_{R^o_{SD}}(S_i, D_j)) \qquad (11.6)$$

In a similar manner, relation degrees are computed between symptom combinations and diseases, namely:

$$\mu_{R^5_{PD}}(P_q, D_j), \mu_{R^6_{PD}}(P_q, D_j), \mu_{R^7_{PD}}(P_q, D_j), \mu_{R^8_{PD}}(P_q, D_j) \tag{11.7}$$

Symptom combinations being logical combinations of symptoms, these values are computed using the basic formulas:

$$\mu_{\xi_i \wedge \xi_j} = min(\mu_{\xi_i}, \mu_{\xi_j})$$
$$\mu_{\xi_i \vee \xi_j} = max(\mu_{\xi_i}, \mu_{\xi_j})$$
$$\mu_{not\xi_i} = 1 - \mu_{\xi_i}$$

The confirmed diagnoses are all D_j for which:

$\mu_{R_2}(P_q, D_j) = 1.00$ or $\mu_{R_6}(P_q, D_j) = 1.00$

All D_j are displayed as excluded diagnosis if either:

$\mu_{R_3}(P_q, D_j) = 1.00$ or $\mu_{R_4}(P_q, D_j) = 1.00$ or $\mu_{R_7}(P_q, D_j) = 1.00$ or $\mu_{R_8}(P_q, D_j) = 1.00$

Finally, all diagnoses D_j are diagnostic hypotheses if either:

$max(\mu_{R_1}(P_q, D_j), \mu_{R_2}(P_q, D_j)) > 0.50$ or
$max(\mu_{R_5}(P_q, D_j), \mu_{R_6}(P_q, D_j)) > 0.50$

For instance, in the example presented above, CADIAG-2 finds that D_1 and D_2 are not confirmed or excluded diagnoses, but rather are diagnostic hypotheses. It will propose to perform the synovial fluid examination, since finding S_8 would prove D_2 as the correct diagnosis.

11.2.3 NUTRI-EXPERT: diet monitoring

11.2.3.1 Introduction. Nutri-Expert is an educational software which has been designed in cooperation with the Diabetology Department of the Toulouse Hospitals. It helps patients to improve their nutritional habits, by analysing in detail their food intakes, and by suggesting changes that result in well balanced meals. Medical experiments made on more than 1500 subjects have shown that an unsupervised 6 month use of the software improved very significantly the patients' knowledge on nutrition and their cooking habits, and even improved significantly several physiological indicators such as blood glucose [50].

Nutri-Expert can be used as a stand-alone micro-computer program, or as a Java client. It has been extensively used for six years, one reason of this success being that it is used directly by the patient, and that it performs a task (namely balancing daily meals) which no medical practitionner would want to make. Indeed, the physician prescribes the main points of the patient's nutrition plan, and the nutritionist gives advices and sometimes describes some typical meals, but the patient at home is alone to buy, cook and eat its own foods. Thus Nutri-Expert is situated at an important and previously vacant place into the therapeutic process.

Nutri-Expert is composed of several modules closely linked together. The main one is the analysis module, which allows the patient to analyse a particular meal and get it well balanced. It uses a custom made food composition database of 1550 foods, permanently updated by a pool of nutritionists. It gives the values of 32 nutriments, for all the common cooked and raw ordinary foods and the most common dishes in France. Databases adapted to other European countries as well as North America are in progress.

11.2.3.2 Dealing with imprecise data. There are two different sources of imprecision or fuzziness in Nutri-Expert. The first is the food composition database, where some values are imprecisely known, sometimes even completely unknown. For instance, there is only one entry for apple in the database although there are several species of apple on sale, which can all be at various stages of maturity. In this case, imprecision is a result of the averaging of several values. For other foods, the values of some nutriments have not been measured, and the nutritionists must still express what they know about it, even with much imprecision or fuzziness.

The second source of imprecision comes from the patient, when he must feed the analysis module with the weights of his meals' foods. If the weights of some packaged items are precisely known (yogurts, etc.), all other foods must be either weighted with a kitchen scale or described in terms of portions.

Contrary to most other systems, there is no uncertainty to deal with in Nutri-Expert. Values stored or provided are imprecise or fuzzy, but certain, and there is no inference process per-se which introduces uncertainty. Fuzzy arithmetic is used extensively, to perform computation as well as to compare values and perform pattern-matching.

11.2.3.3 Representation of imprecise or fuzzy numbers and intervals. Fuzzy intervals [26] are used in Nutri-Expert to represent numbers (the values describing the meal) as well as intervals (the norms the meal must satisfy).

Fuzzy intervals allow Nutri-Expert to be pessimistic and optimistic at the same time: the support of the interval is chosen large enough to be sure that no value is unduly excluded, and the core represents the most plausible values.

What is of primary importance is to determine the set of values which are completely impossible (for which the membership degree is equal to 0) and the set of values which are completely possible (for which the membership degree is equal to 1); the remaining subsets of the domain correspond to gradual transitions. Possibility theory is not very sensitive to slight variations of the possibility degrees; what really matters is that if a value is considered more possible than another one for a variable, then a greater possibility degree must be assigned to the former value.

In other words, the piecewise linear function between the core of the fuzzy interval and its support will cope with the desired robustness.

From a computational point of view, such intervals are modeled by 4-tuples ([26]): (l, r, dl, dr) where $[l, r]$ is the core and $[l - dl, r + dr]$ is the support of the fuzzy interval.

11.2.3.4 Elicitation of data from the patient. Asking the patient anything about the imprecision of his foods' weights has seemed unrealistic. When a user gives a weight value, Nutri-Expert looks up in the food database if it is a packaged item or not. If so, the weight is assumed to be a precise number, represented by a fuzzy interval $(m, m, 0, 0)$. If it is not a packaged item, the program checks if the weight has been given as a number of portions or in grams. A number of portions is assumed to imply a greater imprecision. In both cases, the precise value given by the patient is transformed into a fuzzy value, using a transforming function associated to the food and the portion/gram choice, the name of which is stored in the food database. Presently there are 15 different such functions. For instance, the $f/10/20$ function is associated to the bread's weight when expressed as a number of slices, and transforms a weight x into the fuzzy interval $(x - 10\%, x + 10\%, x * 20\%, x * 20\%)$.

As for the values stored in the food composition database, they are all fuzzy numbers, and the nutritionists have been instructed how to deal with them. A value is stored as a precise number, along with a transforming function such as the above f/10/20; the set of transforming function has been elaborated by the nutritionists themselves. When a value field is left blank, it means that absolutely nothing is known on the value. It corresponds to a possibility distribution uniformly equals to 1, which can be implemented by the fuzzy interval $(-\infty, +\infty, +\infty, +\infty)$. For instance, it is often the case for calcium in commercial foods. The total amount of calcium in a meal containing such foods can still be estimated, and the resulting imprecision will affect its upper bound.

11.2.4 Fuzzy arithmetic

Nutri-Expert needs the four basic arithmetic operations to perform its computations. It has been proved that, for continuous monotonous functions, including arithmetic operations (on the subdomains where they are monotonic), we have:

$$(M * N)_\alpha = M_\alpha * N_\alpha = \{u * v | u \in M_\alpha, v \in N_\alpha\} \tag{11.8}$$

For multiplication and division, an approximation must be made, otherwise the result is no longer trapezoidal. The most important parts of the result, namely the core and the support, can be calculated exactly, and a straight line is drawn between them on both sides to get a trapezoid-shaped result again. This approximation will leave unchanged the order of the membership values in $]0, 1[$ (see [18] for the detailed formulas).

11.2.5 Fuzzy pattern matching

Using fuzzy arithmetic as described above, the program is able to compute assessments on a set of nutriments, leading to a vector of data $D_1, D_2, ...D_n$. Each D_i is a fuzzy interval, which must be compared to a corresponding norm P_i, and the different pattern matching indices must be aggregated in order to assess to normality of the whole meal.

It has been established with the medical team that the different norms P_i are also fuzzy intervals. For instance, for an ordinary lunch and for all kinds of medical diseases, they told that "the fat percentage of the caloric goal must be approximately between 25% and 35%". They added that 20% and 40% where clearly out of the norm, so their statement could be translated into the following trapezoid-shaped fuzzy interval: $(5, 25, 35, 5)$.

Two scalar measures are used in Nutri-Expert in order to estimate the compatibility between a pattern P and a data D: a degree of possibility of matching $\Pi(P; D)$ and a degree of necessity of matching $N(P; D)$ which are respectively defined by (see [26]):

$$\Pi(P; D) = \sup_{u \in U} min(\mu_P(u), \mu_D(u)) \tag{11.9}$$

$$N(P; D) = \inf_{u \in U} max(\mu_P(u), 1 - \mu_D(u)) \tag{11.10}$$

$\Pi(P; D)$ is a degree of overlapping of the fuzzy set of values compatible with P, with the fuzzy set of values compatible with D. $N(P; D)$ is a degree of inclusion of the set of values compatible with D into the set of values compatible with P.

The computation of $\Pi(P; D)$ and $N(P; D)$ on trapezoid-shaped intervals is a matter of lines intersection (see [18] for a complete description).

11.2.6 Global matching evaluation

A set of indices $\Pi(P_i; N_i)$ and $N(P_i; N_i)$ can be computed when matching separately each data of the set $D_1, D_2, ..., D_n$ with the corresponding pattern of the set $P_1, P_2, ..., P_n$. Each D_i and P_i were defined above as an assessment and its corresponding norm for each nutriment considered for the balance of the meal.

Since the involved variables are independent (i.e., the fuzzy set of values compatible with a variable does not depend on the value given to another variable), and if it is supposed that all parts of the pattern have an equal importance, an aggregation of the different measures is (see [26]):

$$\Pi(P_1 \times ... \times P_n; D_1 \times ... \times D_n) = \min_{i=1,n} \Pi(P_i; D_i) \tag{11.11}$$

$$N(P_1 \times ... \times P_n; D_1 \times ... \times D_n) = \min_{i=1,n} N(P_i; D_i) \tag{11.12}$$

where $\times$ denotes the Cartesian product defined for fuzzy sets by

$$\forall u_i \in U_i, \forall u_j \in U_j, \quad \mu_{P_i \times P_j}(u_i, u_j) = min(\mu_{P_i}(u_i), \mu_{P_j}(u_j)) \tag{11.13}$$

This aggregation using the 'min' operation preserves the respective semantics of possibility and necessity degrees.

Yet in the particular case of Nutri-Expert, the different variables have not an equal importance. According to the medical team, the fat, carbohydrate and protein percentage and the caloric intake are by far the most important variables. As for the others, it depends very much on the kind of meal and of the particular medical problems of the patient: some variable may be as important as the first four, and others may be completely unimportant.

Let $w_1, w_2, ..., w_n$ be the grade of importance of patterns $P_1, P_2, ..., P_n$ respectively. It is supposed that $\forall i, \ w_i \in [0, 1]$, the greater w_i the greater the importance of P_i; we also assume that $\max_{i=1,n} w_i = 1$ (normalization), i.e., the most important patterns are graded by 1. Then if s_i denotes a degree of matching of a datum (possibility or necessity) with respect to the atomic pattern P_i, the corresponding degree of matching s_i of this datum with respect to the whole pattern $(P_1, P_2, ..., P_n)$, taking into account the importance assessement, will be given by (see [26, 28]):

$$s = \min_{i=1,n} \max(1 - w_i, s_i) \tag{11.14}$$

Note that if all the w_i's are equal to 1 (equal importance), we get $s = \min_{i=1,n} s_i$; when $w_i = 0$, the matching degree with the pattern P_i is not taken into account.

The implementation in Nutri-Expert of this weighted fuzzy pattern matching technique has been quite simple, and takes place in two stages. A two dimensional array indicates for each kind of meal and for each nutriment the norm pattern to use, and its weight in the global matching. Then the program takes into account the possible medical problems of the patient in the following way. For each disease of the patient (he may have several) and for each nutriment, another two dimensional array specifies a new norm pattern and a new weight, which may override a previous constraint of the first stage.

Finally, a meal is said well balanced if the global pattern matching with the 'well balanced' norm patterns leads to $\Pi = 1$ and $N \geq 0.7$. Otherwise, Nutri-Expert makes a comment for each nutriment responsible for the unbalance. The threshold 0.7 has been empirically adjusted in relation with the medical group.

11.2.6.1 A heuristic search algorithm to balance a meal. After having pointed out the unbalanced nutriments, the main task of Nutri-Expert is to indicate to the patients how to modify the meal to get it well balanced, and adapted to their medical problems (for a diabetic for instance, the glucide intake must be in narrower ranges than for other people). But patients happen to be generally unable to get a meal well balanced by themselves. The task is indeed a difficult one, because modifying the weight of a food often leads to unbalance several nutriments at the same time.

The problem may seem linear, and solvable using classical techniques, but several points make it impossible. First the linear equations to solve have fuzzy terms. Second, the food weights to compute must be compatible with food portions. Third, some foods are forbidden for some people; others have to be replaced. The problem is much more of an operational kind, and the notion of possible actions on a meal has emerged as central. These operations can be parametered by tables, setting average quantities, portions and accommodations according to diseases. Then the meal entered by the patient with these rules generates a space of derived meals where the solution is to be found.

Heuristic search is a well known method to cleverly visit such a state space in order to find a solution that matches the constraints [42]. The search graph is only potentially defined, in the sense that only the root is explicitly available, together with a set of rules which specify how to build the successors of a current node.

Using applicable rules on some node ("the father") creates new nodes ("the sons"), together with an arc from the father to each son. This is called node expansion. Each arc is valuated by a cost which is supposedly a positive number. The cost of a path is the sum of the costs of its arcs. An optimal solution corresponds to a minimal cost path from the root to a goal node. The tree search methodology consists in applying rules, where possible, to nodes until a goal node is reached. As long as a goal node is not reached, the main problem is to select the proper node to be expanded.

This choice can be driven by the knowledge of a so-called evaluation function f so that its value, $f(n)$, at ant node n estimates the sum of the cost from the root to node n (denoted $g(n)$) and the minimal cost from node n to a goal state (denoted $h(n)$). Let $h^*(n)$ be the cost of an optimal path from n to t. Upper and lower bounds of $f^*(n)$ are denoted $\overline{f}(n)$ and $\underline{f}(n)$ respectively. An upper bound of $f^*(n)$ is the cost of the corresponding path and can be used to reduce the width of the search graph by pruning pending (= not expanded yet) nodes n' such that $\overline{f}(n) \leq \underline{f}(n')$. An estimate $f(n)$ which is not established as an upper or lower bound is called heuristic.

If $h(n) \leq h^*(n)$ then such an algorithm is called A^* by Nilsson [42]. It terminates in a finite number of steps, and provides an optimal path (exit 5) or such a path does not exist (exit 3). The algorithm is then said to be admissible. When $h(n)$ is only heuristic, then the optimality of a solution discovered by the algorithm is no longer guaranteed. However, the use of a heuristic evaluation may enable such a solution to be discovered faster than using a bad lower bound $\underline{h}(n)$ (for instance, $\underline{h}(n) = 0$ only produces a uniform-cost algorithm).

Dubois, Farreny and Prade [25] presented an extension of the basic A^* algorithm which tries to synthetize all the available information concerning the value of $h^*(n)$ (in particular the knowledge of a lower bound $\underline{h}(n)$), with a fuzzy interval, in order to allow for a more elaborate reordering of the potential nodes to expand.

11.2.6.2 Choice of an heuristic. The first version of the balancing algorithm used the following forward estimation function [18]:

$$h(meal) = \frac{\sum_{i=1,p}(1 - N_i)}{2} \tag{11.15}$$

where N_i is the matching necessity degree of the hypothetical meal n with the norm pattern of nutriment i, for the p nutriments involved for the patient. This formula is based on the experimentally observed fact that a randomely chosen action performed on a randomly chosen meal gives way to two nutriment mismatches, on average.

$f(n)$ is clearly heuristic, and the algorithm is not of the A^* kind. From a set of about 3480 real patients' meals, this first algorithm found a solution for about 2510 meals. 'finding a solution' here means finding a node which satisfy the constraints after less than 1000 trials. The main problem of this heuristic is that it characterizes how much wrong is the meal rather than it estimates the cost to the closest solution.

Recently, a new forward estimation has been used [19]:

$$h(meal) = \max_{n \in nutriments} \Delta_n(n, goal(n)) \tag{11.16}$$

where $\Delta_n(n, goal(n))$ estimates the minimum cost, in number of operations, it demands for improving the nutriment n, in other words, the number of operations it takes to have this nutriment normalized using the better food for it.

The 'max' in (11.16) is a 'fuzzy max' of the fuzzy interval Δ_n [26]. Such an operation can be very hard to work out completly.

A simplified version of this new heuristic has recently been implemented in Nutri-Expert [19]. From the test database of 3480 meals, 3060 meals are now corrected. Most of the 420 remaining meals have a minimal cost to improve them so high that it is very difficult to reach the solution within the 1000 trials.

11.2.7 RENOIR/MILORD

RENOIR [11] aids the nonspecialized physician in diagnosing arthritis and collagen diseases. It is a rule-based expert-system which has been programmed using the MILORD environment [33], and its knowledge base contains more than 1000 rules. Uncertainty is modeled in MILORD by fuzzy intervals representing the meaning of linguistic certainty values. These labels are a closed set of choices for the user to express his confidence in the data he is introducing in the system. They are preferred to scalar uncertainty factors, the authors arguing that most physicians are unable to make a fair estimation of the inaccuracy of their judgments, making far larger estimation errors that the boundaries accepted by themselves as feasible. All computations are based on possibility theory, and many compatibility degrees are computed off-line, since the number of combinaisons of linguistic labels is finite.

Here is an example of an inference process with MILORD:

- IF
  1. Community acquired pneumonia is almost sure
  2. Bacterial disease is possible
  3. (No aspiration) is very possible
- THEN Enterobacteria is quite possible

Observed facts:

1'. Community acquired pneumonia is very possible

2'. Bacterial disease is almost sure

3'. Aspiration is slightly possible

Inference steps:

a. Compatibility between (1) and (1') gives: moderately possible

b. Compatibility between (2) and (2') gives: almost sure

c. Negation of (3'): (no aspiration) is very possible

d. Compatibility between (3) and (c) gives: possible

e. [(a) and (b) and (d)] gives: moderately possible

f. Inference: (e) and the rule value (possible) gives: moderately possible

g. Composition between (f) and the conclusion label (quite possible) gives: possible

11.2.8 Cardioanaesthesia monitoring

An example of fuzzy rule based systems oriented towards mediacl process control rather than diagnosis is provided by an alarm system in cardioanaesthesia [8, 9, 10] which helps the anesthesist to manage the stabilisation of the patient's haemodynamic state during open-heart surgery. The system works on-line, gathering all required data from a general anaesthesia information system. It supports monitoring of five haemodynamic 'state variables', which are estimated by the intelligent alarm system using fuzzy rules. There are approximately 50 rules for each 'state variable', which have been acquired from 13 anaesthesists.

The input and output parameters of the alarm system are transformed into 'linguistic variables' and their terms corresponding to their linguistic use in anaesthesia. The terms are 'too low', 'a little too low', 'good', 'a little too high', 'too high'. The fuzzification transforms the vital parameters into linguistic variables using these membership functions. Rules are then used to compute a result, and a defuzzification into a crisp output value is performed by the 'center of gravity' method. The five state values are displayed as colored bars on a monitoring equipment situated in front of the anaesthesist.

An example of a rule is: "if systolic arterial pressure is a little too high, and left atrial pressure is too low, then myocardial contractility is good". To the rule is also associated a value of support between 0 and 1.

The acquisition of the membership functions used during the fuzzification step has been made by summing up for each fuzzy label the ranges given by ten experienced anesthesists, each having a weight of 1/10.

11.2.9 Other Systems

11.2.9.1 PROTIS and SPHINX. The rule-based system PROTIS [47, 46] gives therapeutic advice to nonspecialized physicians about non insulo-dependent diabetic patients.

A rule in PROTIS has the following form:

FR: $< condition > \rightarrow < decision > (e, r)$

$< decision >$ is an element in a finite set of possible decisions; e and r are respectively called suggestion degree and rejection degree, and have the following meaning:

- the more e is near 1 and the more $< condition >$ is satisfied, the more $< decision >$ is confirmed
- the more r is near 1 and the more $< condition >$ is satisfied, the more $< decision >$ is rejected

Rule conditions are a combination of elementary conditions, using the $\wedge$ and $\vee$ connectors. Elementary conditions are represented by possibility distributions, among three classes of predefined shapes. Facts are also represented by possibility distributions of a parabolic shape, modelling imprecision and fuzziness, but not uncertainty.

A fuzzy pattern matching [20] is made between known facts and elementary conditions, leading to possibility and necessity degrees which are combined using min and max for conjunctions and disjunctions of conditions respectively (so no compensation or differences in relative importance are allowed).

For a rule 'FR: $c \rightarrow d(e, r)$' whose condition c is satisfied with the possibility and necessity degrees P and N respectively, PROTIS computes the two following indices:

$\alpha = \max(0, P - (1 - e))$: evocation degree of d by c

$\beta = \min(1, N + (1 - r))$: rejection degree of d by c

When several rules give several α_i and β_i for the same decision d, they are combined into $\alpha = \max_i \alpha_j$ and $\beta = \min_i \beta_i$. Like MYCIN, this kind of blind combination may lead to confusing results for conflicting or non independent rules.

There is only one level of rules; after the inference process, PROTIS displays for the physician the possible therapeutic decisions with their associated evocation and rejection degrees.

An interesting feature in PROTIS is the presence of meta-rules which allow the translation of condition possibility distributions in particular situations, or the modify the weights e and r. It permits for instance to take into account the exceptions of a rule by forcing to (0,1) the weights (e, r).

The rule-based system SPHINX [32, 46] has been applied to diabetes and icterus. Rules in SPHINX have the same form and meaning as in PROTIS. The inference process is almost exactly the same, leading to evocation and rejection degrees computed as above, with the difference that P and N are replaced by a single number t, called semantic conformity degree, computed in an ad-hoc manner.

11.2.9.2 AUDIGON. AUDIGON [34] makes a diagnosis of osteaoarthrosis, based on MR-images of the knee. The knee cartilage is segmented in small regions, and 80 membership values CF from 15 different features are automatically extracted from the image, for each region. The diagnostic process can then be started from this symbolic description.

It is implemented using fuzzy rules with a min-max inference. Here is an example of a rule and its use:

certainty factor("segment-grade-1-damaged") =
min (CF(slightly contrasted),
1 - CF(little thickness),
CF(surface very smooth),
CF(surrounding intensity values slightly higher),
CF(small contrast in the surrounding))

The certainty factors are computed for each segment and inserted into three-dimensional maps.

11.2.9.3 Ultasonic prenatal examination and digital mammography. These are applications where programs work from medical images, and try to detect or reject abnormal measurements.

For prenatal examination, a simple fuzzy inference [48] has been implemented for classifying a foetus as normal, slightly abnormal or abnormal, based on measurements of head circumference, abdominal circumference, and femur length.

In mammography analysis [38, 14], the meaning of terms such as 'size of undulations', 'deepness of lobularity' and others are redefined as fuzzy subsets. The related primitives are automatically extracted from a mammogram, and a mass found is classified as lobulated or microlobulated, by combining the various membership degrees using the 'min' operator.

11.2.9.4 Cancer radiotherapy. Another type of applications in cancer radiotherapy aims at defining the target-volume to be irridiated [52]. This volume must be chosen large enough to enclose the whole tumor including all the microscopic tumor cell spread. On the other hand, the surrounding healthy tissues have to be spared as much as possible.

Diagnostic imaging techniques are not sensitive and specific enough to visualize all individual tumor cells infiltrating the normal tissues beyond the boundaries of the visible gross tumor mass. Due to this lack of information, different interpretations among radiotherapists are justifiable concerning the extent of the planning target volume (PTV) for certain tumor types. This can be interpreted as fuzziness of the target volume.

Medical images are segmented into voxels (smallest volume elements), and an automatic estimatation for each voxel of the value of TCP (Tumor Control Probability) and NTCP (Normal Tissue Complication Probability) is made. A NTCP of 5% is considered as the maximum acceptable complication risk, whereas TCP must be as near 1 as possible. These two values are transformed into linguistic fuzzy labels, and fuzzy rules using the max-min inference are applied in order to estimate the membership degree of the considered voxel to PTV.

The center of gravity defuzzification with symmetrically extended outer sets is then performed, and the results are displayed using 3D-plots.

11.2.9.5 Diagnostic of diabetes using glucose tolerance test. Some systems have an output which is a matter of degree of intensity (rather than an output with a certainty level). This is the case of the system [6] which considers diabetes as a fuzzy concept, and proposes a diagnostic process using a fuzzy inference from data gathered during the glucose tolerance test. This test consists of measuring blood glucose 6 times, every 30 minutes after a 75g of dextrol intake. For a given time t_k (k: 0, 30, 60, 90, 120, 180), a set of rules of the kind "if the level of BG is comparatively large and the IRI is comparatively small, then the patient is diagnosed as moderately diabetic".

11.2.9.6 EMERGE. EMERGE [35] is an expert system for the analysis of patient complaints in the emergency room environment. The system has been successfully evaluated on 179 retrospective cases and 100 prospective cases. Each symptom, sign or test result may be present to a certain degree, modeled as a membership value into a fuzzy subset. Each elementary condition may have a particular weight in the antecedent of a rule. A conjunction is evaluated as:

$$\sum_{i=1}^{n} w_i * c_i \tag{11.17}$$

where w_i is the weight of a condition and c_i is its degree of presence. So a relative compensation is made between conditions, contrary to the standard use of 'min'. The firing of a rule is determined by the degree of presence s of its antecedent exceeding a threshold. The value s becomes the certainty factor associated with that rule.

11.2.9.7 Diagnostic interpretation of electrocardiograms. A electrocardiogram interpretation has been performed, first based on medical rules and on automatically extracted signal features[13]. The imprecision in data and rule antecedents and the uncertainty of rule conclusions are managed in the framework of the fuzzy set theory, and a 'best fit' method is used to linguistically express fuzzy and uncertain results with words used in the cardiology community.

Recently, the same diagnostic interpretation has been made using a neural network with a fuzzy preprocessing stage[45]. A study based on a large validation database of ECG signals has been performed, and has shown a very good diagnostic accuracy.

11.2.9.8 Diagnosis of Nephropathia Epidemica. An architecture for a generic tool which supports data analysis and development of diagnostic modules in clinical medicine has been developed[31]. It uses a fuzzy neural net architecture with only one layer, which is fed with data from a preprocessing fuzzifying module. This approach has been applied to the diagnosis of Nephropathia Epidemica, and proved the importance of the preprocessing stage.

11.2.9.9 Closed-loop delivery of muscle relaxant. A model-based controller for the closed-loop delivery of a muscle relaxant has been realised, relying on a model of the process under control[37]. The resulting system has been shown to perform well under simulated and real conditions.

11.3 CONCLUDING DISCUSSION

Most medical facts, from symptoms to conclusions, are related to variables whose domains are continous. Often when the domain is reduced to a set of finite values, an oversimplification is made. In a previous work[17], we had been working on the diagnosis of diabetes and its classification in two classical categories, namely insulino-dependent diabetes and non insulino-dependent diabetes. It appeared later than this dichotomy was more blurred than we had thought, and that each type of diabetes was indeed a fuzzy category.

MYCIN dealt only with finite sets of values for its clinical parameters, and it leads unavoidably to sudden changes of conclusions when input data are modified continuously. However, it allowed a simple and efficient representation of uncertainty, and even ignorance.

CADIAG-2 deals only with continuous variables, for symptoms as well as diagnoses. But they are represented and stored as a single membership value for a set of predefined fuzzy entities, and a lot of information is lost in this process. Moreover, the model does not permit to represent ignorance, and ad-hoc means have to be used.

Thorough comparisons have been made in [21, 29] between CADIAG-2 and MYCIN. [21] has shown how CADIAG-2 can be embedded into MYCIN-like systems, and proposed an approach of inclusion of negative knowledge into CADIAG-2.

As advocated in [16], possibility distributions can store all kinds of information available on a variable, in a simple and computationaly efficient way. Imprecision, fuzziness, uncertainty and even ignorance can be represented in a straightforward way, as well as pieces of information which are both imprecise and uncertain: 'X is A is certain to the degree $1 - \epsilon$'

$$\pi_X(u) = max(\mu_A(u), \epsilon) \tag{11.18}$$

where ϵ stands for the level of possibility of being outside of A

When dealing with a conjunction of independent conditions, formula (11.11) should be used, or (11.14) if the conditions have not an equal importance. However, we have seen with the EMERGE system that sometimes, physicians allow a compensation between conditions, and then an additive combinaison such as (11.17) must be used.

The possibilistic framework also offers representation capabilities for expressing different kinds of rules including purely gradual rules (of the form 'the more X is A, the more Y is B'), and rules whose condition parts may also be a matter of degree, but whose conclusions are pervaded with uncertainty [30], as well as nonmonotonic reasoning capabilities for managing rules with exceptions having different levels of specificity [12].

In all the reviewed systems, fuzzy set theory, even when used in a rather elementary way, improved significantly the quality of the programs, by taking into account the inherent uncertainty and imprecision of both data and medical knowledge. Thus the results can change gradually with data, and there are no more discontinuity near thresholds or when reaching the border of a class of values (Nutri-Expert). Uncertainty can be elicited in a qualitative way, and qualitative results can also be obtained (MILORD, CADIAG-2, etc.). Finally, many medical norms which are crisply defined can be flexibly expressed in a more natural way (e.g. in cardioanesthesia alarms, prenatal examinations, mammography analysis).

The interest of researchers in knowledge-based systems in medicine has apparently somewhat declined in the last ten years, whereas mathematical frameworks such as fuzzy sets and possibility theory are now ready to handle problems in a sound and efficient way. In a near future, computerized patients' records will be available at the physicians's desks, and this will create a need for new developments.

References

[1] Adlassnig K.-P., Kolarz G. (1982). CADIAG-2: Computer-assisted medical diagnosis using fuzzy subsets. In: M.M. Gupta and E. Sanchez (Eds.) Approximate Reasoning in Decision Analysis, 219-247, North-Holland Publishing Company, 1982.

[2] Adlassnig K.-P. (1982). A survey on medical diagnosis and fuzzy subsets. In: M.M. Gupta and E. Sanchez (Eds.) Approximate Reasoning in Decision Analysis, 203-217, North-Holland Publishing Company, 1982.

[3] Adlassnig K.-P. (1986). Fuzzy set theory in medical diagnosis. IEEE Transactions on Systems, Man and Cybernetics SMC-16, 260-265.

[4] Adlassnig K.-P. (1990). Update on CADIAG-2: a fuzzy medical expert system for general internal medicine. In: W. H. Janko et al. (Eds.) Progress in Fuzzy Sets ans Systems, 1-6, Kluwer Academic Publishers, Netherlands, 1990.

[5] Adlassnig K.-P. (1991). Knowledge acquisition study and accuracy rate evaluation for CADIAG-2/RHEUMA with 308 clinical cases, Proc. Med. Inform. Eur. 1991, 332-336, Springer-Verlag, Vienna, 1991.

[6] Arita S., Yoneda M., Hori Y. (1993) Supporting system for the diagnosis of diabetes mellitus based on glucose tolerance test responses using a fuzzy inference. In: R. Lowen and M. Roubens (Eds.) Fuzzy Logic, 301-310, Kluwer Academic Publishers, Netherlands, 1993.

[7] Barreiro A., Mira J, Marin R., Delgado A.E., Couselo J.M. (1990). Fuzzy knowledge representation for leukemia diagnosis in children oncology. In: W. H. Kanko et al. (Eds.) Progress in Fuzzy Sets and Systems, 22-34.

[8] Becker K., Käsmacher H., Juffernbruch K., Rau G., Kalff G., Zimmermann H.-J. (1993) An intelligent alarm system for decision-support in cardioanesthesia: knowledge base and user interface. Proc. First European Congress on Fuzzy and Intelligent Technologies (EUFIT'93), 1023-1026, Aachen, Sept. 7-10, 1993.

[9] Becker K., Käsmacher H., Rau G., Kalff G., Zimmermann H.-J. (1994) A fuzzy logic approach to intelligent alarms in cardioanesthesia. Proc. Int. Conf. on Fuzzy Systems IEEE 1994, 2072-2076.

[10] Becker K., Thull B., Käsmacher-Leidinger H., Stemmer J., Rau G., Kalff G., Zimmermann H.-J. (1997) Design and validation of an intelligent patient monitoring and alarm system based on a fuzzy logic process model. Artificial Intelligence in Medicine, 11, 33-53.

[11] Belmonte-Serrano M., Sierra C., López de Mántaras R. (1994). RENOIR: An expert system using fuzzy logic for rheumatology diagnosis. International Journal of Intelligent Systems, 9, 985-1000.

[12] Ben Ferhat S., Dubois, D., Prade H. (1998). Practical handling of exception-tainted rules and independence information in possibilistic logic. Applied Intelligence, 9, 101-127.

[13] Bortolan G., Degani R. (1988). Linguistic approximation of fuzzy certainty factors in computerized electrocardiography. In: M.M. Gupta, T. Yamakawa (Eds.) Fuzzy Computing, North-Holland, 243-261.

[14] Bothorel S., Bouchon Meunier B., Muller S. (1997). A fuzzy logic based approach for semiological analysis of microcalcifications in mammographic images. International Journal of Intelligent Systems, 12, 819-848.

[15] Buchanan G. G., Shortliffe E. H. (1984). Rule-based expert systems. The MYCIN experiments of the Stanford Heuristic Programming Project, Addison-Wesley, Reading.

[16] Buisson J.-C., Farreny H., Prade H. (1985). The development of a medical expert system and the treatment of imprecision in the framework of possibility theory. Information Sciences, 37, 211-226, 1985.

[17] Buisson J.-C., Farreny H., Prade H., Turnin M.C., Tauber J.P., Bayard F. (1987). Toulmed, an inference engine which deals with imprecise and uncertain aspects of medical knowledge. Proc. European Conference on Artificial Intelligence in Medicine (AIME 87), In: J. Fox, M. Fieschi, R. Engelbrecht (Eds.) Lecture Notes in Medical Informatics, 33, 123-140, Springer-Verlag, 1987.

[18] Buisson J.-C. (1997). Nutri-Expert, an educational software in nutrition. International Journal of Intelligent Systems, 12, 915-933.

[19] Buisson J.-C., Garel A. (1998) Balancing meals using fuzzy arithmetic and heuristic search algorithms, Int. Rep. IRIT.

[20] Cayrol M., Farreny H., Prade H. (1980). Fuzzy pattern matching. Kybernetes, 11, 103-116.

[21] Daniel M., Hajek P., Nguyen P.H. (1997). CADIAG-2 and MYCIN-like systems. Artificial Intelligence in Medicine, 9, 241-259.

[22] Deutsch-McLeish M., Yao P. (1991). Further work on modelling uncertainty in medical diagnosis using belief functions. Workshop Proc. of the North American Fuzzy Information Processing Society (NAFIPS'91), 131-136, 1991.

[23] Deutsch-McLeish M., Mukherjee S.K. (1993). A fuzzy deductive database for handling uncertain information in the field of medical diagnosis. Proc. Fifth IFSA World Congress, 42-45, 1993.

[24] Dubois D., Prade H. (1980). Fuzzy sets and systems: theory and applications, Academic Press, New-York.

[25] Dubois D., Farreny H., Prade H. (1987). Combinatorial search with fuzzy estimates. In J. Kacprzyk, S.A. Orlovski (eds.), Optimization Models Using Fuzzy Sets and Possibility Theory, 171-185.

[26] Dubois D., Prade H. (1988) (with the collaboration of H. Farreny, R. Martin-Clouaire, C. Testemale). Possibility theory - An approach to the computerized processing of information. Plenum Press, New-York.

[27] Dubois D., Prade H. (1988) Representation and combinaison of uncertainty with belief functions and possibility measures. Comput. Intell., 4, 244-264.

[28] Dubois D., Prade H. Testemale C. (1988) Weighted fuzzy pattern matching, Fuzzy Sets and Systems, 28, 313-331.

[29] Dubois D., Lang J., Prade H. (1991) Fuzzy sets in approximate reasoning, Part 2: Logical approaches. Fuzzy Sets and Systems, 40, 203-244.

[30] Dubois D., Prade H. (1996) What are fuzzy rules and how to use them. Fuzzy Sets and Systems, 84, 169-185.

[31] Eklund P., Fogström M., Forsström J. (1992). A generic neuro-fuzzy tool for developing medical decision support. Proceeding of the MEPP'92, Abo Akademi Press, Abo, 11-27.

[32] Fieschi M., Joubert M., Fieschi D., Soula G., Roux M. (1982). Sphinx: an interactive system for medical diagnosis aids. In: M.M. Gupta and E. Sanchez (Eds.) Approximate Reasoning in Decision Analysis, North-Holland, 1982.

[33] Godo L., López de Mántaras R., Sierra C, Verdaguer A. (1989). MILORD: The architecture and the management of linguistically expressed uncertainty. International Journal of Intelligent Systems., vol. 4, 471-501.

[34] Heller B., Schlegelmilch S. (1993) HYPERCON - A framework of modular knowledge bases for the HYPERtension CONsultation., Proc. First European Congress on Fuzzy and Intelligent Technologies (EUFIT'93), 415-419, Aachen, Sept. 7-10, 1993.

[35] Hudson D. L., Cohen M. E. (1986) Management of uncertainty in a medical expert system. In: B. Bouchon and R.R. Yager (Eds.) Uncertainty in Knowledge-Based Systems., 283-293, Springer-Verlag, 1986.

[36] Hudson D. L., Cohen M. E., Anderson M. F. (1992) Approximate reasoning with if-then-else rules in a medical expert system, International Journal of Intelligent Systems, 7, 71-79.

[37] Kern S.E., Johnson J.O., Westenskow D.R. (1997) Fuzzy logic for model adaptation of a pharmacokinetic-based closed loop delivery system for pancuronium. Artificial Intelligence in Medicine, 11, 9-31.

[38] Kovalerchuk B., Triantaphyllou E., Ruiz J. F., Clayton J. (1996). Fuzzy logic in digital mammography: analysis of lobulation. Proc. Int. Conf. on Fuzzy Systems IEEE 1996, 1726-1731.

[39] Kovalerchuk B., Triantaphyllou E., Ruiz J. F., Clayton J. (1997). Fuzzy logic in computer-aided breast cancer diagnosis: analysis of lobulation. Artificial Intelligence in Medicine, 11, 75-85.

[40] Nguyen, H. P. (1995). Approach to combining negative and positive evidence in CADIAG-2. Proc. European Congress on Fuzzy and Intelligent Technologies (EUFIT'95), 1653-1658.

[41] Nguyen, H. T. (1978). A note on the extension principle for fuzzy sets. J. Math. Anal. Appl., 64, n∘2, 369-380.

[42] Nilsson, N. (1980). Principles of artificial intelligence. Tioga Pub. Co., Palo Alto, Ca.

[43] Shortliffe E. H. (1976). Computer-based medical consultation, MYCIN, Elsevier/North-Holland, New-York, 1976.

[44] Sanchez E. (1998). Fuzzy logic and inflammatory protein variations. Clinica Chimica Acta, 270, 31-42.

[45] Silipo R., Bortolan G., Marchesi C. (1995). Fuzzy proprocessing and artificial neural networks classification for the diagnostic interpretation of resting ECG. In: A. Murray, R. Arzbaecher (Eds.) Computers in Cardiology 95, IEEE Computer Society, Los Alamitos, 365-368.

[46] Soula G., Sanchez E. (1982). Soft deduction rules in medical diagnosis processes. In: M.M. Gupta and E. Sanchez (Eds.) Approximate Reasoning in Decision Analysis, North-Holland, 77-88, 1982.

[47] Soula G., Vialettes B., San Marco J.L. (1983). PROTIS, a fuzzy deduction-rule system: application to the treatment of diabetes. Proc. MEDINFO 83, Amsterdam, 533-255.

[48] Smith B. J., Arabshahi P. (1996). A fuzzy decision system for ultrasonic prenatal examination enhancement. Proc. Int. Conf. on Fuzzy Systems IEEE 1996, 1712-1717.

[49] Steinmann F. (1997). Fuzzy set theory in medicine. Artificial Intelligence in Medicine, 11, 1-7.

[50] Turnin M.C., Beddok R., Clottes J, Abadie R., Martini P., Buisson J.C., Soule-Dupuy C., Bayard F., Tauber J.P. (1992). Telematic expert system Diabeto : a new tool for diet self monitoring for diabetic patients. Diabetes Care, 15 (2).

[51] Van Melle W. (1979). A domain-independant production-rule system for consultation programs. Proc. IVth IJCAI Tokyo, Aug. 1979, 923-925.

[52] Waschek T., Levegrun S., Schlegel W., Van Kampen M., Engenhart-Cabillic R. (1996). Target volume definition for three-dimensional radiotherapy of cancer patients with a fuzzy rule based system. Proc. Int. Conf. on Fuzzy Systems IEEE 1996, 1719-1725.

[53] Weierich P., Wetzel D., Niemann H. (1993) AUDIGON - A medical expert system with new judgement functions for the fuzzy rulebase. Proc. First European Congress on Fuzzy and Intelligent Technologies (EUFIT'93), 472-477, Aachen, Sept. 7-10, 1993.

[54] Yager R. R. (1986). Paths of least resistance in possibilistic production systems. Fuzzy Sets and Systems, 19, 121-132.

[55] Ying H., Sheppard L., Tucker D. Fuzzy control of arterial oxygen using a fuzzy expert system shell FLOPS., Proc. of the 7th Annual Meeting of the North American Fuzzy Information Processing Society (NAFIPS'88), 296-300, 1988.

[56] Zadeh, L.A., (1975). The concept of a linguistic variable and its application to approximate reasoning. Information Sciences, Part 1 : 8, 199-249, Part 2 : 8, 301-357; Part 3 : 9, 43-80.

[57] Zadeh L.A. (1978). Fuzzy sets as a basis for a theory of possibility. Fuzzy Sets and Systems, 1 (1), 3-28.

[58] Zadeh L.A. (1979). A theory of approximate reasoning. Machine Intelligence, vol. 9 (Hayes J.E., Michie D., Mikulich L.I. Eds.), 149-194, New-York, Elsevier, 1979.

[59] Zahan S., Michael C., Nikolakeas S. (1996). Fuzzy hierarchical approach to medical diagnosis - An application to the myocardial ischemia diagnosis. Proc. European Congress on Fuzzy and Intelligent Technologies (EUFIT'96), 2081-2085.

[60] Zahan S., Michael C., Nikolakeas S. (1997). A fuzzy hierarchical approach to medical diagnosis. Proc. Int. Conf. on Fuzzy Systems IEEE 1997, 319-324.

[61] Zimmermann H.-J., Zysno P. (1980). Latent connectives in human decision making. Fuzzy Sets and Systems, 4, 37-51, 1980.