

# Using Fuzzy Evidential Reasoning for Multiple Assessment Fusion in Spondylarthropathic Patient Self-management

Giovanni Schiboni, Wolfgang Leister and Liming Chen

**Abstract** This paper proposes an approach for an ICT-supported medical assessment, by merging measures of signs and symptoms from heterogeneous sources. The disease status estimate of patients that suffer from spondylarthropathy is evaluated with different types of uncertainties using a fuzzy rule-based evidential reasoning (FURBER) approach. The approach treats measures of signs and symptoms in order to define the disease status. We take in consideration the Bath indices and the ASDAS index, described by using fuzzy linguistic variables. A fuzzy rule-base designed on the basis of a belief structure is exploited to capture uncertainty and non-linear relationships between these parameters and the disease status. The inference of the rule-based system is implemented using an evidential reasoning algorithm. An expected utility-based health score is used to assess disease activity over time and to measure the response to treatment. Our tool may be particularly helpful in monitoring the response of treatments and in interpreting the response to therapeutic interventions in clinical trials. A case study is used to illustrate the application of the proposed approach.

**Keywords** Spondyloarthritis · Medical assessment · Multiple attribute decision analysis · Fuzzy rule-base · Utility · Evidential reasoning · Uncertainty modelling

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# 1 Introduction

The spondyloarthropathies (SpA) are a group of related conditions that includes ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), undifferentiated spondyloarthropathy and inflammatory, bowel-disease-associated arthritis. Collectively, these arthropathies are characterized by inflammatory arthritis, extra-articular inflammation, preceding bacterial infection, seronegativity for rheumatoid factor and a strong HLA-B27 association [10]. Usually, there is no definite direction for SpA assessment. Outcome measurement in SpA, particularly AS, has been a rapidly growing field over the last decade, with enormous progress being made in patient-reported outcomes, clinical assessments, physical measurements and composite scoring of disease state, and response to treatment. The purpose is to perform a process for determining a *SpA disease status estimate* from a subject through signs and symptoms of the disease. Signs are directly discovered by the physician or by health monitoring systems [28] and symptoms are obtained from a patient's experience and feelings. The acquisition of signs and symptoms knowledge implies uncertain measures. Acquisition systems need to be tolerant against sensor failures while being able to deal with a high degree of uncertainty arising from the open world setup. Further, patients cannot describe exact conditions. Consequently, the medical decision making process is dominated by uncertainty [20]. Thus, inevitably, the main problem for constructing an accurate and complete mathematical model for a disease status assessment is representation of uncertainty.

Rationally, reliably, and correctly handling uncertainties in medical diagnosis and treatment decisions are major challenges that have been researched more than four decades [21]. The first well-known medical rule based expert system [37] was used to diagnose bacterial infections. Several frameworks have been proposed [4, 9, 14, 22, 30, 36, 43] but all of them have a lack of procedures to address uncertainty, relying heavily on supporting statistical information that may not be available. Note well this list is not exhaustive.

One way to deal with information that may be imprecise, ill-defined, and incomplete, for which traditional quantitative approaches (e.g., statistical approach) do not give an adequate answer, is the incorporation of subjective and/or vague terms, i.e., linguistic assessments instead of numerical values. Fuzzy logic approaches [55], employing fuzzy IF-THEN rules (where the conditional part and the conclusions contain linguistic variables [58]), can model the qualitative aspects of human knowledge and the reasoning process without employing precise quantitative analysis. This provides a tool for working directly with the linguistic variables, when a communication process is involved between medical expert and patient.

A linguistic variable for a fuzzy set [59] is a variable for whose values are words (or linguistic terms) rather than numbers. Each linguistic variable represents a universal set and the different linguistic terms are fuzzy sets in the universal set. The different terms or linguistic values are also characterized by membership functions defined on the universe of discourse [1].

The fuzzy encoding of signs and symptoms of a SpA disease status estimate well suits with the approximate reasoning for medical assessment. The motivations are clear from the characteristics of linguistic variables:

- linguistic variables may be regarded as a form of information compression called granulation [56];
- they serve as a means of approximate characterization of phenomena that are either too ill-defined, too complex, or both, to permit a description in sharp terms [57];
- they provide a means for translating linguistic descriptions into numerical and computable ones. Therefore, the duality between symbolic and numerical processing becomes natural instead of antagonistic [12].

In view of the complexity of a mathematical model for such purpose, the knowledge representation power of fuzzy rule-based systems is severely limited if only fuzziness is taken into account in representing uncertain knowledge. In a SpA disease status estimate, intrinsically vague information may coexist with conditions of *lack of specificity* originating from evidence not strong enough to completely support a hypothesis but only with degrees of belief or credibility [2]. This could come from erroneous measures of sensor failures or from a degree of ignorance of an expert. Dempster-Shafer (D-S) theory of evidence [6, 34], based on the concept of belief function, is well suited to modeling subjective credibility induced by partial evidence [41]. The D-S theory describes and handles uncertainties using the concept of the degrees of belief, which can model incompleteness and ignorance explicitly. It also provides appropriate methods for computing belief functions for combination of evidences [29]. Besides, the D-S theory also shows great potentials in multiple attribute decision analysis (MADA), where an evidential reasoning (ER) approach for MADA has been developed, on the basis of a distributed assessment framework and the evidence combination rule of the D-S theory [46, 49–51, 53, 54]. The combination may become substantial when a lack of specificity in data is prevalent. In these cases, experts may have difficulty in structuring and articulating causal relationships [23].

A Belief Rule Base (BRB) for a Clinical Decision Support Systems (CDSS) architecture to make clinical decision, disease suspicion or diagnosis has been developed recently. This BRB CDSS employed three layers architecture with BRB framework, which allows the handling of various types of uncertainty found in clinical domain knowledge as well as clinical and medical data. They applied a rule-base inference using the evidential reasoning approach, i.e., RIMER [47] and fuzzy logic [46, 49, 51]. The same RIMER approach has been applied for the design, development and application of an expert system to diagnose influenza under uncertainty [35].

In this paper, we describe an approach for modeling a SpA disease status that is based on fuzzy logic and the evidential reasoning approach. In order to deal with fuzziness and incompleteness in the assessment, we use a fuzzy rule-based evidential reasoning (FURBER) approach [25]. In our approach, signs and symptoms parameters are described by using fuzzy linguistic variables and the outcomes of a fuzzy rule-base, or consequents, with belief structure, describe the disease status.

The fuzzy rules with belief degrees are used to capture uncertainty and causal relationships between the signs and symptoms and the disease status. To the best of our knowledge, this is the first time that a fuzzy BRB is used, in conjunction with the evidential reasoning, in order to perform a SpA assessment, addressed as a MADA problem. This BRB with fuzzy logic approach gives us the ability to handle both vague information and ignorance or incompleteness due to evidence which is not strong enough to make simple true or false judgments, but with degrees of belief. In fact, the approach brings the following advantages both in:

- *Encoding gathered informations.* It allows to take in consideration vagueness or fuzzy uncertainty in the description of SpA signs and symptoms, using subjective and vague linguistic terms which may overlap in their meanings instead of independent crisp sets. For example, the assessment grades ‘Moderate’ and ‘Severe’ are difficult to be expressed as clearly distinctive crisp sets, but quite natural to be defined as two dependent fuzzy sets. In other words, the intersection of the two fuzzy sets may not be empty.
- *Decoding a consistent estimate as result of the assessment process.* In real-life diagnosis, a doctor cannot judge one patient disease status to be 100 % consistent with the actual level of the disease. Opinion or judgment with belief levels must be expressed. For example: “Severe” outcome from the Bath indices is consistent with a high degree of belief of SpA disease with a 80 % probability; “Moderate Disease Activity” from ASDAS outcome is a medium degree of belief of SpA disease with a 60 % probability. Hence, the probability of a degree of SpA disease for the patient can be High, Medium or Low with different degrees of belief. From the above, it can be inferred that the uncertain knowledge that exists with the SpA assessment should need to be processed by using refined knowledge representation schema and inference mechanism.

Our expert system is designed to be the assessment module of a personalized Chronic Patient Self-Management System (CPSMS) for SpA [32].

## 2 A Fuzzy Evidential Reasoning Based Approach to Multiple Assessment Fusion

The CPSMS is an ontology-based decision support system with the goal of improving the quality of life (QoL) of the patients by facilitating patients with chronic disease to carry out personalized self-management. Based on personalized rules for training and using a disease and training diary, the patients will be given recommendations to handle their disease in self-management. It is done via knowledge description and inference for both patients and their conditions by providing a set of non-pharmacological treatment plans or suggestions.

To support the CPSMS, it is necessary to predict an individual’s SpA disease status based on a combination of physiological, behavioral and psychological features. A

quantitative clinical analysis of the status of patients with musculoskeletal disorder throughout their stay in a domestic environment has to be performed. The disease states are correlated to non-invasive objective (physiological, behavioral) and subjective (psychological) assessment measurements. Trends in disease states through the course of treatment can then be tracked. The combination of different complementary metrics, based on the measures, would be in the study of response to treatment in clinical spondyloarthritis. While behavioral symptoms are all highly discriminative in predicting a state of suffering, they have traditionally been very qualitative in nature. Using sensor and mobile technology, we would be able to precisely and quantitatively measure these symptoms, in order to develop objective diagnostic assessments. In addition, to have a more reliable measure of the patient status, the physiological/contextual measures will be sustained by subjective outcomes from clinical psychological measures in the form of questionnaires. To this end, this paper develops a fusion model which integrates physiological and behavioral measures, with the ultimate purpose of accurately determining the disease status of a SpA patient as well as trending the effects of treatment. Using these objective scales, in fact, it's possible to have clinically significant outcomes related to a subject's state, marked at different spaced intervals, throughout the course of the treatment. The performance of a treatment and the quantification of a subject's progress over time would be then feasible, by exploiting an automated tracking of the patient's response to treatment over time. Thus, quantitatively measuring the degree of change in the measures, allows to evaluate the degree of response in treatment.

The process of modeling our SpA medical assessment comprises the following four elements, each described in detail in their corresponding section: (1) identification of measures of symptoms; (2) definition of the input and fuzzy variables; (3) the fuzzy rule-based belief structure, and (4) the rule-based inference mechanism.

## 2.1 *Identification of Measures of Symptoms*

In order to obtain a SpA disease status estimate, we consider analysis of Bath indices and ASDAS index outcomes, demonstrating the procedure involved in the inference process. In Table 1 the list of measures of symptoms considered is presented.

The Bath indices [13] present outcome measures from SpA patients and comprise of four indices:

- BASMI, the Bath AS Metrology Index;
- BASFI, the Bath AS Functional Index;
- BASDAI, the Bath AS Disease Activity Index;
- BAS-G, the Bath AS Patient Global Score.

The BASMI quantifies the mobility of the axial skeleton in AS patients and allows objective assessment of clinically significant changes in spinal movement. The index is determined by clinical measures of cervical rotation, tragus to wall distance, lumbar flexion, lumbar side flexion, and intermalleolar distance.

**Table 1** Measures of symptoms and their characteristics

Test	Measure	Content	Response	Scale	References
BASMI	Objective	Sensor based	Numerical	0–10	Jenkinson et al. [18]
BASFI	Self-reported	Questionnaires	Likert	0–10	Calin et al. [3]
BASDAI	Self-reported	Questionnaires	Likert	0–10	Garrett et al. [11]
BAS-G	Self-reported	Questionnaires	Likert	0–10	Jones et al. [19]
ASDAS (CRP)	Hybrid	Questionnaires/lab analysis	Numerical	0–∞	Lukas et al. [26]

The BASFI defines and monitors physical functioning of patients with AS. The index is determined by eight items concerning activities referring to the functional anatomy of the patients (bending, reaching, changing position, standing, turning, and climbing steps), and two items assessing the patients' ability to cope with everyday life.

The BASDAI measures patient-reported disease activity in patients with AS. The index is determined by patient-reported levels of back pain, fatigue, peripheral joint pain and swelling, localized tenderness, and the duration and severity of morning stiffness.

The BAS-G gives a global assessment of the well-being of the person with AS over a given time period. The index is determined by two visual analog scales to measure the effect of AS on the respondent's well-being, the first estimated over the last week, the second over the last 6 months.

The subjective measures have a numeric response scale (0–10) anchored by adjectival descriptors as a Likert scale.

The Ankylosing Spondylitis Disease Activity Score (ASDAS) measures disease activity in AS based on a composite score of domains relevant to patients and clinicians, including both self-reported items and objective measures. The index is determined by patient-reported assessments of back pain, duration of morning stiffness, peripheral joint pain and/or swelling, general well-being, and a serologic marker of inflammation (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]). ASDAS has a continuous scale from zero with no defined upper end. A clinically important change is present when a difference of 1.1 units or greater appears; a major change is defined as a change of 2.0 units or more [27]. More information about these measures of symptoms can be found in literature [60].

## 2.2 Definition of the Input and Fuzzy Variables

A granularity of linguistic terms sets, used for describing each fundamental attribute, i.e., measures of symptoms, has to be defined, according to its own qualitative characteristics, i.e., linguistic terms or assessment grades, and quantitative characteristics,

i.e., numerical scales. Subjective assessments are more appropriate for SpA analysis by using these parameters, as they are always associated with great uncertainty, since they come from imprecise source of knowledge, as questionnaires. Each has its own set of fuzzy assessment grades, fuzzy grades for short, characterized by linguistic variables, instead of precise numbers in probabilistic terms, and by fuzzy membership functions (FMFs). A total of  $N = 5$  variables must be defined in terms of fuzzy grades. In general, attributes  $e_i$ , with  $i = 1 \dots 5$  are described by  $j_i$  fuzzy grades  $\{A_{i,j}, j = 1 \dots j_i\}$ , respectively. Thus, a type of FMF has to be selected for each attribute description. There is some flexibility defining FMFs depending on experts considerations. The application of categorical judgements is suitable in terms of the nature of our source of informations.

As far as BASMI ( $e_1$ ), BASFI ( $e_2$ ), BASDAI ( $e_3$ ) and BAS-G ( $e_4$ ) are concerned, we follow the granularity of the respective questionnaires, i.e., ‘Very Severe’ (VS), ‘Severe’ (SE), ‘Moderate’ (MO), ‘Mild’ (MI), and ‘None’ (NO), as well agreed in the medical community.

In compact notation:

$$\{A_{i,j}, i = 1 \dots 4 \text{ and } j = 1 \dots j_i\} = \{NO, MI, MO, SE, VS\}, \quad (1)$$

where  $j_i = 5$ .

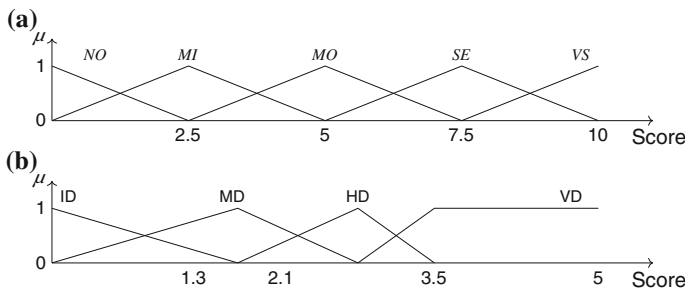
Figure 1a shows an example for the FMFs definition. The choice of the FMFs has to be done by expert-knowledge.

As far as the ASDAS index ( $e_5$ ) is concerned, the choice of the fuzzy grades comes from [27], where the following disease activity states are described: ‘Very High Disease’ (VD), ‘High Disease Activity’ (HD), ‘Moderate Disease Activity’ (MD), ‘Inactive Disease Activity’ (ID). In compact notation:

$$\{A_{5,j}, j = 1 \dots j_5\} = \{ID, MD, HD, VD\}, \quad (2)$$

where  $j_5 = 4$ .

The scale on which the FMFs are distributed is relevant during modeling. In Fig. 1b, for example, the scale is different from the other attributes, according to the



**Fig. 1** a FMFs for assessment grades and  $e_1, e_2, e_3$  and  $e_4$ . b FMFs for assessment grades for  $e_5$

definition of the ASDAS index. Note that the straight-line FMFs are just chosen for their simplicity. More complex, e.g., non-linear FMFs could be used, according to different kinds of information sources considered and to the different requirements. If numerical values from the measures scores above are not available at all, then the modeling can also be carried out only based on subjective judgements, following this granularity. Furthermore, the belief distribution assessment scheme, proposed in Sect. 3, permits inference even in case no FMF is available.

Now, let us assume that the *SpA disease status estimate* of a patient, i.e., output of the assessment, can be classified into several categories (grades) of values. Our choice, for describing linguistically the assessment uses the values as consequent variable: ‘High’ (Hi,  $C_4$ ), ‘Medium’ (Me,  $C_3$ ), ‘Low’ (Lo,  $C_2$ ) and ‘None’ (No,  $C_1$ ).

In compact notation:

$$\{C_j, j = 1 \dots j_c\} = \{No, Lo, Me, Hi\}, \quad (3)$$

where  $j_c = 4$ .

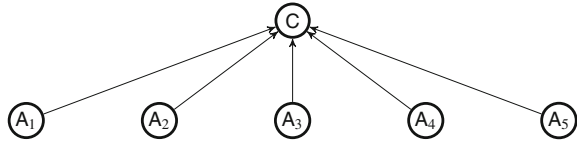
### 2.3 Construct a Fuzzy Rule-Base with the Belief Structure

Let us define a rule-based system for receiving information from different assessments and inferring conclusions. This step is the knowledge-based core of the approach since it merges the various heterogeneous assessment measures coming from the different sensorial assessments. The set of rules has to be defined by domain experts and observation facts. It is a reasoning scheme provided to the model as a priori.

The key constituents are the IF-THEN rules, extended with belief degrees, in which each antecedent attribute takes referential values and each possible consequent is associated with belief degrees [46]. The knowledge representation parameters, i.e., the rule weights, antecedent attribute weights and belief degrees with consequents, are extended by incorporating the concept of belief rule into fuzzy IF-THEN rules for a SpA medical assessment:

$$\begin{aligned} R_k : & \text{ if } (e_1 \text{ is } A_1^k) \wedge \dots \wedge (e_N \text{ is } A_N^k), \\ & \text{ then } \{(C_1, \bar{\beta}_{1,k}) \dots (C_{j_c}, \bar{\beta}_{j_c,k})\} \\ & \left( \sum_{j=1}^{j_c} \bar{\beta}_{j,k} \leq 1 \right), \text{ with a rule weight } \theta_k \\ & \text{ and attribute weights } \delta_{k,1} \dots \delta_{k,N} \\ & k \in \{1 \dots L\} \end{aligned} \quad (4)$$



**Fig. 2** Evaluation hierarchy

where  $A_i^k$  represents the value of the  $i$ th antecedent attribute  $e_i$  in the  $k$ th rule.  $\bar{\beta}_{j,k}$  is the belief degree to which  $C_j$  is believed to be the consequent if, in the  $k$ th packet rule, the input satisfies the packet antecedents  $A^k = \{A_1^k \dots A_N^k\}$ . If  $\sum_{j=1}^{j_c} \bar{\beta}_{j,k} = 1$  the  $k$ th rule is said to be complete, otherwise it is incomplete.

The schema of this belief rule base is depicted in Fig. 2. It represents the logic framework of the reasoning process. A bottom-up paradigm is used to solve the inference. In the first layer, the antecedents  $A_i$ , with  $i = 1 \dots N$ , represent pieces of evidence for the rules. Such information is then aggregated using the ER approach in Sect. 3.4, obtaining the consequents outcome  $C$ .

### 3 The Fuzzy Evidential Inference Mechanism for Multiple Assessment Fusion

Once a rule-base is established, the knowledge contained can be used to perform inference for the given input. The inference procedure is composed of different components that are: (1) input transformation, (2) rule activation weight calculation, (3) rule update mechanism, (4) aggregation of the rules, (5) expected utility definition. In Sect. 3.1, we describe the way in which the input for an antecedent can be decoded into a distribution representation of the linguistic terms using belief degrees. In Sect. 3.2, we describe how to compute the total degree to which the input matches to the packet antecedents. In other words, how to quantify the contribution of each rule, through the weights of activation, for the subsequent aggregation process. In Sect. 3.3, we describe how to handle incomplete information due to a lack of data. In Sect. 3.4, we describe the evidential reasoning algorithm. Eventually in Sect. 3.5, we describe how to extract a health score from the distributed assessment, output of the ER, exploiting the concept of expected utility.

#### 3.1 Input Transformation

Inputs are discretized into a distributed representation of linguistic terms in antecedents using belief degrees. The general input form corresponding to the antecedent attribute in the  $k$ th rule is:

$$(A_1^*, \varepsilon_1) \wedge \dots \wedge (A_5^*, \varepsilon_5) \quad (5)$$

where  $A_i^*$  is the actual input for the attribute  $e_i$ ,  $\varepsilon_i$  is the degree of belief assigned by an expert to the association of  $A_i^*$ . A distribution assessment approach [25, 47, 49] permits to assess the input  $(A_i^*, \varepsilon_i)$  for an antecedent  $e_i$  to a distribution representation of the linguistic terms using belief degrees:

$$S(e_i) = S(A_i^*, \varepsilon_i) = \{(A_{i,j}, \alpha_{i,j}), j = 1 \dots j_i\} \quad (6)$$

for  $i = 1 \dots N$ , where  $A_{i,j}$  is the  $j$ th linguistic value;  $\alpha_{i,j}$  is the belief degree to which the input  $(A_i^*, \varepsilon_i)$  for  $e_i$  belongs to the linguistic value  $A_{i,j}$  with  $\alpha_{i,j} \geq 0$  and  $\sum_{j=1}^{j_i} \alpha_{i,j} \leq 1$ .

Consider that  $\alpha_{i,j}$  in Eq. 6 can be generated in different ways depending on the nature of the antecedent attribute and the availability of data [25, 38]. Due to the possible uncertainty in the inputs, for the purpose of a disease status modeling, it is assumed that each input parameter ( $e_i$  with  $i = 1 \dots N$ ) could be presented in terms of FMF (if it is available) in any of the following forms based on available information, history data or expert experience:

- A single deterministic value with 100 % certainty.
- A closed interval defined by an equally likely range.
- A triangular distribution defined by a most likely value, with lower and upper least likely values.
- A trapezoidal distribution defined by a most likely range, with lower and upper least likely values.

If the measures of symptoms are the same as identified in Sect. 2.1, the main scenario is the one in which a numerical score  $x_i$  is provided for each  $e_i$ . In this case there is the need to calculate the distributed assessment of  $x_i$ , relative to the  $i$ th attribute, on the fuzzy grades  $A_{i,j}$  [52]. This can be done by defining its degrees of belief for which it belongs to the fuzzy grades by normalizing its membership degrees to these grades. Thus, firstly, the membership degrees of  $x_i$  must be computed on the assessment grades (see Fig. 1b) correspondent to attribute  $i$ . This is simply done applying the formula:

$$\mu_{i,j} = \begin{cases} 0, & x_i \leq a \\ \frac{x_i - a}{b - a}, & a \leq x_i \leq b, \\ \frac{c - x_i}{c - b}, & b \leq x_i \leq c, \\ 0, & c \leq x_i, \end{cases} \quad (7)$$

for  $j = 1 \dots J_i$

where  $\mu_{i,j}$  is the degree of membership of the triangular FMF relative to the  $j$ th term of the  $i$ th attribute and  $a, b, c$  are the parameters of the FMF. To obtain the distributed assessment of an original score  $x_i$  on the  $i$ th attribute, these membership degrees are normalized to generate its degrees of belief as follows:

$$\begin{aligned}
\alpha_{i,j} &= \frac{\mu_{i,j}}{\mu_{i,j} + \mu_{i,j+1}} \\
\alpha_{i,j+1} &= \frac{\mu_{i,j+1}}{\mu_{i,j} + \mu_{i,j+1}} \\
\text{for } j &= 1 \dots j_i - 1
\end{aligned} \tag{8}$$

Note that if the requirement of mutual complementarities for the FMFs is satisfied  $\alpha_{i,j} = \mu_{i,j}$ .

If the input parameters, instead, correspond to forms 2, 3 or 4,  $\alpha_{i,j}$  can be formulated as follows [25]:

$$\begin{aligned}
\alpha_{i,j} &= \frac{\tau(A_i^*, A_{i,j})\varepsilon_i}{\sum_{j=1}^{j_i} [\tau(A_i^*, A_{i,j})]}, \\
\text{for } i &= 1 \dots N \text{ and } j = 1 \dots j_i
\end{aligned} \tag{9}$$

where  $(A_i^*, \varepsilon_i)$  is the actual input corresponding to the  $i$ th antecedent,  $\tau$  is a matching function,  $\tau(A_i^*, A_{i,j}) = \tau_{ij}$  is a matching degree to which  $A_i^*$  belongs to  $A_{i,j}$ . Note that, even if  $A_i^*$  completely belongs to the  $j$ th linguistic expression, i.e.,  $\tau(A_i^*, A_{i,j}) = 1$ ,  $\alpha_{i,j} \neq 1$  if  $\varepsilon_i \neq 1$ .

Other matching functions can be employed [47]. For qualitative parameters, for example, a subjective numerical scale may be used against which the range of parameters is mapped. A medical judgement, coming from the doctor, or physiologist, experience and records, could be included in the assessment process.

### 3.2 Rule Activation Weight Calculation

Consider an input as in Eq. 5 corresponding to the  $k$ th rule as defined in Eq. 4

$$e_1 \text{ is } (A_1^k, \alpha_1^k) \wedge \dots \wedge e_5 \text{ is } (A_5^k, \alpha_5^k)$$

where  $A_i^k \in \{A_{i,j}, j = 1 \dots j_i\}$  and  $\alpha_i^k \in \{\alpha_{i,j}, j = 1 \dots j_i\}$  is the individual belief degree that the input belongs to  $A_i^k$  of the individual antecedent  $e_i$  appearing in the  $k$ th rule. The total degree  $\alpha_k$  to which the input matches to the packet antecedent  $A^k$  in the  $k$ th rule is defined by combining the individual degrees  $\alpha_i^k$  for  $i = 1 \dots N$  [25]. The weight of activation of the  $k$ th rule  $w_k$  is computed by exploiting the flowing formula [33]:

$$w_k = \frac{\theta_k \alpha_k}{\sum_{j=1}^L \theta_j \alpha_j} = \frac{\theta_k \prod_{i=1}^N (\alpha_i^k)^{\delta_{ki}}}{\sum_{j=1}^L \theta_j [\prod_{l=1}^N (\alpha_l^j)^{\delta_{jl}}]} \tag{10}$$

with

$$\bar{\delta}_{ki} = \frac{\delta_{ki}}{\max_{l=1 \dots N} \{\delta_{kl}\}}. \quad (11)$$

Here  $\bar{\delta}_{ki}$  is the relative weight of  $A_i^k$  used in the  $k$ th rule, obtained by dividing the weight of  $A_i^k$  with maximum weight of all the antecedent attributes of the  $k$ th rule. This normalized value  $\bar{\delta}_{ki}$  implies that the range of its value is between 0 and 1. Finally, consider that  $\alpha_k = \prod_{i=1}^N (\alpha_i^k)^{\bar{\delta}_{ki}}$  is the combined matching degree that is computed by using multiplicative aggregation function. It can be used since the rules are composed only by  $\wedge$  operators.

### 3.3 Rule Update Mechanism

The rule update mechanism is incorporated in an update of the original belief degree  $\bar{\beta}_{ik}$ . When the  $k$ th rule is activated, the consequent of a rule could be incomplete due to the lack of data of the antecedents. If there is an incomplete input for an attribute, it will produce an incomplete output in each of the rules where the attribute is used. So the original belief degree  $\bar{\beta}_{j,k}$  in the  $j$ th consequent  $C_j$  of the  $k$ th rule must be updated based on the actual input information available [33, 40]. The original belief degree is updated as follows:

$$\beta_{j,k} = \frac{\bar{\beta}_{j,k} \left[ \sum_{i=1}^N \xi(i, k) \sum_{t=1}^{j_i} \alpha_{i,t} \right]}{\sum_{i=1}^N \xi(i, k)} \quad (12)$$

where  $\xi(i, k) = \begin{cases} 1, & \text{if } R_k \text{ is used} \\ 0, & \text{otherwise} \end{cases}$

where  $\bar{\beta}_{j,k}$  is given in Eq. 4. Just note that  $0 \leq \beta_{j,k} \leq 1$  for all  $k$  and  $1 - \sum_{j=1}^{j_c} \beta_{j,k}$  denotes both the ignorance incurred in establishing  $R_k$  and the incompleteness that may exist in the input information.

### 3.4 Aggregation of the Rules

Let us consider a fuzzy rule-base with the belief structure that is given by  $R = \{R_1, R_2 \dots R_L\}$ . The  $k$ th rule in Eq. 4 is expressed as:

$R_k$ : if  $e$  is  $A^k$  then *SpA disease status estimate* is  $C$  with belief degree  $\beta_k$

where  $e$  is the antecedent attribute vector  $(e_1 \dots e_N)$ ,  $A^k$  is the packet antecedents  $\{A_1^k \dots A_N^k\}$ ,  $C$  is the consequent vector  $(C_1 \dots C_{j_c})$  and  $\beta_k$  is the vector of the belief

degrees  $(\beta_{1,k} \dots \beta_{j_c,k})$  with  $k \in \{1 \dots L\}$ . The distributed assessment, referred to as a *belief structure* is represented by:

$$S(A^k) = \{(C_i, \beta_{j,k}; j = 1 \dots j_c)\} \quad (13)$$

where  $\beta_{j,k}$  is the degree to which  $C_i$  is the consequent if the input activates the antecedent  $A^k$  in the  $k$ th rule, that is given by Eq. 12 with  $0 \leq \sum_{j=1}^{j_c} \beta_{j,k} \leq 1$  with  $k = 1 \dots L$ .

The ER approach is used to aggregate all the packet antecedents of the  $L$  rules, to obtain the degree of belief of each referential values of the consequent attribute. First, the degrees of belief  $\beta_{j,k}$  for all  $j = 1 \dots j_c$  have to be transformed into basic probability masses [54]:

$$\begin{aligned} m_{j,k} &= w_k \beta_{j,k}, \quad j = 1 \dots j_c \\ m_{C,k} &= 1 - \sum_{j=1}^{j_c} m_{j,k} = 1 - w_k \sum_{j=1}^{j_c} \beta_{j,k} \\ \bar{m}_{C,k} &= 1 - w_k \text{ and } \tilde{m}_{C,k} = w_k (1 - \sum_{j=1}^{j_c} \beta_{j,k}). \end{aligned} \quad (14)$$

with  $m_{C,k} = \bar{m}_{C,k} + \tilde{m}_{C,k}$  for all  $k = 1 \dots L$  and  $\sum_j w_j = 1$ .

All the packet antecedents of the  $L$  rules now can be aggregated to generate the combined degree of belief in each possible consequent term  $C_j$  in  $C$ . Let us consider  $m_{j,I(k)}$  the combined degree of the belief in  $C_j$  by aggregating the first  $k$  packet antecedents  $(A^1 \dots A^k)$  and  $m_{C,I(k)}$  the remaining degree of belief unassigned to any output term. The overall combined degree of belief  $\beta_j$  in  $C_j$  is computed with the evidential algorithm in Eq. 15.

$$\begin{aligned} \{C_j\} : m_{j,I(k+1)} &= K_{I(k+1)} [m_{j,I(k)} m_{j,k+1} + m_{j,I(k)} m_{C,k+1} + m_{C,I(k)} m_{j,k+1}] \\ m_{C,I(k)} &= \bar{m}_{C,I(k)} + \tilde{m}_{C,I(k)}, \quad k = 1 \dots L \\ \{C\} : \tilde{m}_{C,I(k+1)} &= K_{I(k+1)} [\tilde{m}_{C,I(k)} \tilde{m}_{C,k+1} + \tilde{m}_{C,I(k)} \bar{m}_{C,k+1} + \bar{m}_{C,I(k)} \tilde{m}_{C,k+1}] \\ \{C\} : \bar{m}_{C,I(k+1)} &= K_{I(k+1)} [\bar{m}_{C,I(k)} \bar{m}_{C,k+1}] \\ K_{I(k+1)} &= \left[ 1 - \sum_{j=1}^{j_c} \sum_{t=1, t \neq j}^{j_c} m_{j,I(k)} m_{t,k+1} \right]^{-1}, \quad k = 1 \dots L-1 \\ \{C_n\} : \beta_j &= m_{j,I(L)} / (1 - \bar{m}_{C,I(L)}), \quad j = 1 \dots j_c \\ \{C\} : \beta_C &= \tilde{m}_{C,I(L)} / (1 - \bar{m}_{C,I(L)}). \end{aligned} \quad (15)$$

We have that  $\beta_C$  is the belief degree unassigned to any  $C_j$ . It can be proved that  $\sum_{j=1}^N \beta_j + \beta_C = 1$  [54].

The final distributed assessment, which is obtained by aggregating the  $L$  rules activated by the actual input vector  $A^* = \{A^{*k}, k = 1 \dots L\}$  for  $e_i$  with  $i = 1 \dots N$ , is expressed as:

$$S(A^*) = \{(C_j, \beta_j), j = 1 \dots j_c\} \quad (16)$$

The final result is still a belief distribution on disease status estimate, which gives a global view about the SpA disease activity level for a given input.

### 3.5 Expected Utility Definition

Since the aim is to judge the quality of the treatment, i.e., monitoring the status of the patient by assessing if the condition, related to disease activity, deteriorates, remains stable or improves, the trend of the outcomes of assessments needs to be analyzed. Thus, some kind of numerical score, equivalent to the distributed assessment in a sense, must be defined. Expected utility concept can be employed to define such score. Let us consider an utility  $u(C_j)$  of the grade  $C_j$  with

$$\begin{aligned} u(C_{j+1}) &> u(C_j) \\ \text{if } C_{j+1} &\text{ is preferred to } C_j, \end{aligned} \quad (17)$$

where  $u(C_j)$  may be estimated using the probability assignment method [44] or by constructing regression models using partial rankings or pairwise comparison [45]. It is worthy to mention that in [31], they conduct a statistical mapping analysis between a standard investigator assessment of disease severity in AS and domain responses in a standard index of health utility. They implemented the above mapping in an optimized algorithm to estimate utility.

If the assessments are complete and precise, i.e.,  $\beta_C = 0$ , the expected utility of a distributed assessment outcome  $\Phi$  may be considered a *health score* that can be used for ranking assessments. It is calculated as:

$$u(\Phi) = \sum_{j=1}^{j_c} \beta_j u(C_j). \quad (18)$$

An assessment  $\Phi_1$  is preferred to an assessment  $\Phi_2$  if and only if  $u(\Phi_1) > u(\Phi_2)$ . In case the assessment is incomplete, some procedure exists [54] in order to deal with.

## 4 A Case Study in SpA Treatment

The primary target of a SpA treatment is remission of the disease. When it fails, minimizing inflammatory activity of signs and symptoms is the priority, protecting the patient's quality of life by preventing structural damage and functional disability. Therefore, persistence of activity indicates the need for a change of treatment. Our tool may be particularly helpful to monitor patients in a self-monitoring setting. These patients will monitor their health condition, create a log of their condition, and be alerted when changes in their condition does not meet the target, that is their condition is about to worsen. Other applications, such as monitoring the impact of changes in treatment, e.g., in clinical trials are also possible. Since SpA patients react individually to their health condition, one-fit-all recommendations for interpreting the disease activity are not available. Despite this fact, there is a general agreement in the medical community on recommendations for monitoring patients. In particular, the experts agreed that the BASDAI plays a major role in the follow-up of AS [7].

We demonstrate the procedure involved in the FURBER inference for the SpA disease status assessment, by using the following simplified use scenario, similar to the one proposed in [32]. Mark is a SpA patient, male, 25 years old. His SpA disease was confirmed 1 year ago, and now it is under stable condition. He has a regular appointment for treatment at the local clinic every second week. The most obvious symptom for him is back pain and morning stiffness. Usually doctor prescribes pharmacological treatment. With the assistance of the home-based self-management system, he is able to monitor his disease condition on his own. The CPSMS provides Mark with his condition information and both pharmacological and non-pharmacological treatment plans. The CPSMS self-management system tracks the trend of the SpA disease treatment in a period of 8 weeks. The measurements are made every 2 weeks by using mobile phones and sensors and by filling out the Bath and ASDAS questionnaires. In Table 2 outcomes of these measures relative to entire period are presented.

Five levels of linguistic variables are used for Bath indices and four levels for ASDAS index. The definition of their linguistic terms corresponds to the ones in Eqs. 1 and 2 and the corresponding FMF are given in Table 3 and in Fig. 1. Four linguistic expressions are used as well for the consequent variable as the ones in Eq. 3.

### 4.1 Rule-Base with Belief Structure Construction

According to the number of linguistic terms used for describing the antecedents, a rule-base with a total number of 27 fuzzy rules with belief structures is used in the case study, presented in Table 4. The belief degrees that characterize the rule-base are chosen arbitrarily only for illustration purposes, as the actual degrees of belief depend on the context of applications and an expert knowledge is required for their definition. It is worth noting that this is an extremely simplified belief rule-base since

**Table 2** Original measures of symptoms related to a patient and their transformed distributed values

Test	Week 1	Week 3	Week 5	Week 8
BASMI ( $e_1$ )	6 {(MO, 0.6), (SE, 0.4)}	5.3 {(MO, 0.88), (SE, 0.12)}	5.6 {(MO, 0.76), (SE, 0.24)}	4.9 {(MI, 0.04), (MO, 0.96)}
BASFI ( $e_2$ )	5.5 {(MO, 0.8), (SE, 0.2)}	4.9 {(MI, 0.04), (MO, 0.96)}	5.5 {(MO, 0.8), (SE, 0.2)}	4.5 {(MI, 0.2), (MO, 0.8)}
BASDAI ( $e_3$ )	5.8 {(MO, 0.68), (SE, 0.32)}	4.7 {(MI, 0.12)(MO, 0.88)}	5.3 {(MO, 0.88), (SE, 0.12)}	4.4 {(MI, 0.24), (MO, 0.76)}
BAS-G ( $e_4$ )	5.1 {(MO, 0.96), (SE, 0.04)}	4.5 {(MI, 0.2), (MO, 0.8)}	4.8 {(MI, 0.08), (MO, 0.92)}	4.6 {(MI, 0.16), (MO, 0.84)}
ASDAS ( $e_5$ )	2.1 {(MD, 0.64), (HD, 0.36)}	1.5 {(ID, 0.12), (MD, 0.88)}	1.8 {(MD, 0.91), (HD, 0.09)}	1.3 {(ID, 0.24), (MD, 0.76)}

Only non-zero values are presented



**Table 3** Membership functions of the fuzzy assessment grades

Linguistic terms	Bath ( $e_1, e_2, e_3, e_4$ )				
	None ( <i>NO</i> )	Mild ( <i>MI</i> )	Moderate ( <i>MO</i> )	Severe ( <i>SE</i> )	Very severe ( <i>VS</i> )
Grade FMF	(0, 0, 2.5)	(0, 2.5, 5)	(2.5, 5, 7.5)	(5, 7.5, 10)	(7.5, 10, 10)
Linguistic terms	ASDAS ( $e_5$ )				
		Inactive ( <i>ID</i> )	Moderate ( <i>MD</i> )	High ( <i>HD</i> )	Very high ( <i>VD</i> )
Grade FMF		(0, 0, 1.7)	(0, 1.7, 2.8)	(1.7, 2.8, 3.5)	(2.8, 3.5, 5, 5)

in a real-case scenario a higher number of rules would be necessary in order to have a reliable model. Nevertheless, the case study demonstrates that these rules provide a flexible and rational way to construct knowledge base.

## 4.2 Input Transformation

The inputs in Table 2 are transformed into the distributed representation of linguistic terms in the antecedent using Eqs. 7 and 8 based on the corresponding FMF in Table 3 and in Fig. 1. In the rule-base, 27 rules have been defined, of which only a part is fired depending on inputs of different assessments. The fired rules for each assessment are all list in Table 5. The activation weights  $w_k$  of each rule in the fire sub-rule-base are calculated with Eq. 10 where we considered the attribute weights  $\delta_i = 1$  and the rule weight  $\theta_k = 1$ . For an instance, the relative assessment on rule #7 is expressed as:

$$S(A^7) = \{(\text{No}, 0.4), (\text{Lo}, 0.55), (\text{Me}, 0.05), (\text{Hi}, 0)\}$$

with activation weight  $w_7 = 0.0178$  for week 3 global assessment.

## 4.3 Fired Rule Combination Using the ER Algorithm

Exploiting the ER algorithm in Eq. 15 as described in Sect. 3.4 one can aggregate the fired rules and generate a SpA disease status estimate. The distributed assessments, result of the disease status estimate over a period of 8 weeks, are as follows:

**Table 4** Rule-base with belief structure

Rule	Belief				
	Antecedent attributes	Disease status estimate			
		None	Low	Medium	High
R#1	(NO, NO, NO, NO, ID)	1			
R#2	(NO, NO, NO, NO, MD)	0.80	0.20		
R#3	(NO, NO, NO, MI, MD)	0.65	0.35		
R#4	(NO, NO, MI, MI, MD)	0.5	0.5		
R#5	(NO, MI, MI, MI, MD)	0.3	0.7		
R#6	(MO, MI, MI, MO, ID)	0.1	0.5	0.4	
R#7	(SE, MO, MO, MI, MD)	0.4	0.55	0.05	
R#8	(SE, MI, MI, MO, ID)		0.45	0.55	
R#9	(MI, MO, MI, MO, ID)	0.15	0.35	0.5	
R#10	(MO, MI, MO, MI, MD)		0.45	0.55	
R#11	(MI,MI,MO,MO,ID)		0.6	0.4	
R#12	(MI, MI, MI, MI, MD)	0.1	0.9		
R#13	(MI, MI, MI, MI, HD)		0.95	0.05	
R#14	(MI, MI, MI, MO, HD)		0.8	0.2	
R#15	(MI, MI, MO, MO, HD)		0.7	0.3	
R#16	(MI, MI, MO, NO, MD)	0.1	0.5	0.4	
R#17	(MI, MO, MO, MO, HD)		0.55	0.45	
R#18	(MO, MO, MO, MO, HD)		0.35	0.65	
R#19	(MO, MO, MO, MO, VD)		0.15	0.85	
R#20	(MO, MO, MO, SE, VD)			0.9	0.1
R#21	(MO, MO, SE, SE, VD)			0.8	0.2
R#22	(MO, SE, SE, SE, VD)			0.75	0.25
R#23	(SE, SE, SE, SE, VD)			0.6	0.4
R#24	(SE, SE, SE, VS, VD)			0.55	0.45
R#25	(SE, SE, VS, VS, VD)			0.45	0.55
R#26	(SE, VS, VS, VS, VD)			0.25	0.75
R#27	(VS, VS, VS, VS, VD)				1

#### 4.4 Trend Analysis of the Disease Activity During Treatment

The driven paradigm is based on the SpA treat-to-target principles [42]. A therapy plan can be divided into *target change* and *treatment change*. If both non-pharmacological and pharmacological treatments are administered and an assessment result is, after a certain period of time, not on target, then, the treatment plan must be changed accordingly to patient conditions. An instance of target can be that the ASDAS index does not get significantly worse. Thus, it's necessary a health

**Table 5** Fuzzy rule expression matrix of the fired rules for each assessment

Input	Disease status estimate			
	None	Low	Medium	High
<i>Assessment week 1</i>				
$A^{18}(0.2005)$		0.35	0.65	
$A^{19}(0.1128)$		0.15	0.85	
$A^{20}(0.0047)$			0.9	0.1
$A^{21}(0.0022)$			0.8	0.2
<i>Assessment week 3</i>				
$A^6(0.0004)$	0.1	0.5	0.4	
$A^7(0.0178)$	0.4	0.55	0.05	
$A^8(0.0005)$		0.45	0.55	
$A^{10}(0.0055)$		0.45	0.55	
<i>Assessment week 5</i>				
$A^{18}(0.4479)$		0.35	0.65	
$A^{19}(0.0443)$		0.15	0.85	
<i>Assessment week 8</i>				
$A^6(0.0093)$	0.1	0.5	0.4	
$A^9(0.0015)$	0.15	0.35	0.5	
$A^{10}(0.0177)$		0.45	0.55	
$A^{11}(0.0012)$		0.6	0.4	
$A^{12}(0.0002)$	0.1	0.9		

The values in the parentheses are the weights of the packet antecedent attributes  $A^k$  generated using Eq. 10, where we assumed that the weights of rules and the weights of antecedents are equal. Just note that, since the inputs are complete, no update is necessary for the degrees belief

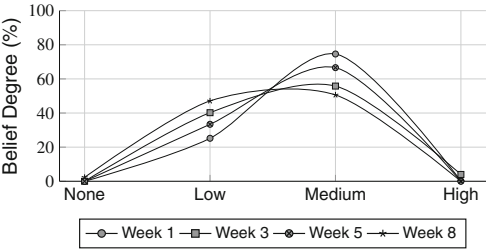
score that measures clinical disease activity at specific time-points for supporting decisions about entry into clinical trials, for supporting treatment changes and for defining therapeutic goals (Fig. 3).

Week 1:  
 $\{(No, 0), (Lo, 0.252), (Me, 0.746), (Hi, 0.002)\}$

Week 3:  
 $\{(No, 0), (Lo, 0.402), (Me, 0.558), (Hi, 0.04)\}$

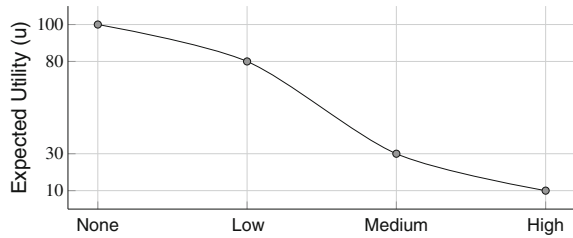
Week 5:  
 $\{(No, 0), (Lo, 0.334), (Me, 0.666), (Hi, 0)\}$

Week 8:  
 $\{(No, 0.023), (Lo, 0.471), (Me, 0.506), (Hi, 0)\}$

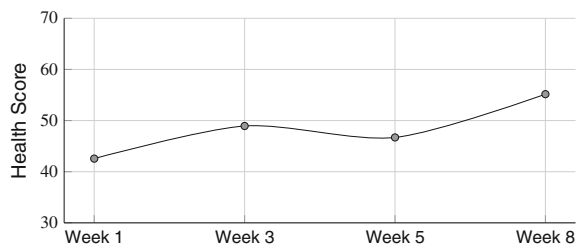


**Fig. 3** Distributed assessments of the SpA disease status in a period of 8 weeks

**Fig. 4** Expected utility defined for assessment grades



**Fig. 5** Health score trend related to SpA disease status in a period of 8 weeks



Following what is described in Sect. 3.5, the expected utilities of individual assessment grades need to be defined first. We defined such expected utility values for different assessment grades, see Fig. 4. More specifically, we assigned an utility score of 100 to grade *No*, 80 to *Lo*, 30 to *Me* and 10 to *Hi*. In this way, a distributed assessment can be transformed to a health score using Eq. 18. Note that a deeper study, made by expert knowledge, should be done in order to define more reliable values.

Finally, applying Eq. 17, health scores can be obtained. Then, their trend can be monitored as depicted in Fig. 3.

In our example, the outcome of the assessment, after a positive response between week 0 and week 3, suggests that Mark's condition is less severe than the situation at the last measurement. Despite the fact that Mark follows doctor's pharmacological and non-pharmacological treatment plans, the disease condition does not get better in the next assessment, between week 3 and week 5, causing a worse response. This would trigger an alert in CPSMS, in order to perform proper updates in its treatment plans (Fig. 5).

## 5 Conclusion and Future Works

In this paper we have described the estimation model of our CPSMS for SpA [32]. The application is supposed to be used in the residential environment of SpA patients, but also to improve communication between patient and health personnel. Solutions of smart monitoring, sensor technologies, objective and subjective assessment, treatment plans, and guidelines are employed.

Our estimation model merges measures of signs and symptoms from heterogeneous sources of information. The disease status estimate of patients, that suffer from spondylarthropathy, is evaluated with different types of uncertainties, using a fuzzy rule-based evidential reasoning (FURBER) approach. A fuzzy rule-base, designed on the basis of a belief structure is exploited to capture uncertainty and non-linear relationships between these measures and the disease status. The approach is able to handle both vague information and ignorance or incompleteness which is not strong enough to make simple true or false judgments but with degrees of belief. Signs and symptoms measures are encoded as distributions on fuzzy linguistic variables, i.e., degrees of belief on assessment grades. Thus, information that come from precise data, random numbers and subjective judgments with uncertainty can be consistently merged under the unified model. Initial case study based on the Bath indices and the ASDAS index showed that such model is able to merge information that comes from disparate sources as other indices, sensor measures, as well as judgement of medical knowledge based on subjective scales. The inference of the rule-based system is implemented using the evidential reasoning algorithm.

The aggregation procedure of the rules preserves the original features of heterogeneous information sources and there is possibility for rule training and self-learning/updating in the rule-base. In fact, it is difficult to determine the elements of a rule-based system entirely subjectively. Also, a change in a rule weight or an attribute weight may lead to significant changes in the performance of a belief rule base. Moreover, the forms of fuzzy membership functions in the antecedent of a rule still remain an important factor for the system performance. For this reason, self-tuning optimal models for belief rule-based systems exist [48]. Based on these optimal models, revised models for self-tuning a FURBER for engineering system safety analysis has been investigated [24]. Supported by real data, in our next work, we'll perform the training of our rule base in an optimal way using expert judgments as well as statistical data. Input data, attribute weights, rule weights, and parameters of fuzzy membership functions will be combined to generate activation weights for rules, and all activated belief rules will be then combined to generate appropriate conclusions using the evidential reasoning approach. Such a combination process is formulated as nonlinear objective functions. The aim is to minimize the differences between observed outputs and the outputs of a BRB, whilst parameter specific limits and partial expert judgments can be formulated as constraints.

Another critical point to evaluate is that, in order to increase interpretability of the disease activity measures, as expressed through health scores, we need some criteria for identifying *improvement scores*. Improvement scores help to determine whether treatments really work, that is whether they actually produce clinically important improvement, allowing investigators, clinicians, regulators and patients to determine the efficacy (or lack thereof) of a given intervention and to communicate about response using the same metric [39]. The interpretation of change in health scores has been a topic of research for almost two decades [15, 17]. It is recognized that the statistical significance of a treatment effect, because of its partial dependency on sample size, does not always correspond to the clinical relevance of the effect. Statistically significant effects are those that occur beyond some level of chance. In contrast,

clinical relevance refers to the benefits derived from that treatment, its impact upon the patient, and its implications for clinical management of the patient [16, 17]. For clinical relevance, one is interested in the *minimally important change* (MIC) of health status questionnaires. Changes in scores exceeding the MIC are clinically relevant by definition [8]. Different methods to determine the minimally important change on the scale of a measurement instrument have been proposed. These methods have been summarized by Crosby et al. [5], by distinguishing distribution-based and anchor-based methods. Criteria for disease activity improvement scores are therefore important for use in clinical practice, observational studies and clinical trials. Such criteria must be developed for our health score. In our real-data experiment we'll have to focus on the evaluation of clinically relevant cut-off values for such improvements scores.

This research has produced a novel tool for decisional support in treatment and self-management for spondylarthropathic patients where the related SpA disease status information is sparse and different kind of uncertainties are involved.

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