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Applying a belief rule-base inference methodology to a guideline-based clinical decision support system

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Abstract: *A critical issue in the clinical decision support system (CDSS) research area is how to represent and reason with both uncertain medical domain knowledge and clinical symptoms to arrive at accurate conclusions. Although a number of methods and tools have been developed in the past two decades for modelling clinical guidelines, few of those modelling methods have capabilities of handling the uncertainties that exist in almost every stage of a clinical decision-making process. This paper describes how to apply a recently developed generic rule-base inference methodology using the evidential reasoning approach (RIMER) to model clinical guidelines and the clinical inference process in a CDSS. In RIMER, a rule base is designed with belief degrees embedded in all possible consequents of a rule. Such a rule base is capable of capturing vagueness, incompleteness and non-linear causal relationships, while traditional IF–THEN rules can be represented as a special case. Inference in such a rule base is implemented using the evidential reasoning approach which has the capability of handling different types and degrees of uncertainty in both medical domain knowledge and clinical symptoms. A case study demonstrates that employing RIMER in developing a guideline-based CDSS is a valid novel approach.*

Keywords: clinical decision support system, clinical guideline, belief rule base, evidential reasoning approach, inference mechanism

1. Introduction

Clinical decision support systems (CDSSs) have almost 40 years of history. From the first generation of CDSSs such as MYCIN (Shortliffe, 1976) to the second generation such as Protégé (Musen *et al.*, 1995), significant research progress, both theoretical and practical, has been made since the idea of computer-based CDSSs first emerged. However, several barriers continue to impede the effective implementation of CDSSs in clinical settings, among which representation of and reasoning about medical knowledge particularly under uncertainty are areas that require refined methodologies and techniques (Lin *et al.*, 2006; Musen *et al.*, 2006). Sources of uncertainty in both medical domain knowledge and clinical symptoms during the process of medical decision making are summarized in Table 1, where all roles involved in medical decision making are listed, and the resultant uncertainties in medical domain knowledge or clinical symptoms related to each role along with their causes are described as

Table 1: *Sources of uncertainty in medical decision making*

Roles involved in medical decision making	*Causes of uncertainty*	*Resultant uncertainties*
Patients	Cannot describe exactly what has happened to them or how they feel	Uncertainties in clinical symptoms
Doctors	Cannot tell exactly what they observe and may produce laboratory results with some degrees of error	Uncertainties in clinical symptoms
Nurses	Cannot tell exactly what they observe	Uncertainties in clinical symptoms
Physiologists	Do not precisely understand how the human body works	Uncertainties in medical domain knowledge
Medical researchers	Cannot precisely characterize how diseases alter the normal functioning of the body	Uncertainties in medical domain knowledge
Pharmacologists	Do not fully understand the mechanisms accounting for the effectiveness of drugs	Uncertainties in medical domain knowledge

Source: Szolovits (1995).

well. As shown in Table 1, uncertainties in both medical domain knowledge and clinical symptoms are unavoidable. One of the main challenges in representation of and reasoning about medical knowledge is how to rationally handle these uncertainties so that a CDSS can support clinicians to make correct and reliable diagnosis and treatment decisions (Lin *et al*., 2006).

In recent years, clinical guidelines which are a format of clinical domain knowledge are increasingly used to improve the quality of care by supporting clinical decision making. While conventional text-based guidelines can only present population-based recommendations which are aimed at a population with one specific disease, guideline-based CDSSs have the potential to provide recommendations aimed at each specific patient (Peleg *et al*., 2003). Studies have shown that computer-based CDSSs, when developed to provide patient-specific assistance in decision making and integrated with clinical workflow, can improve clinicians' compliance with clinical guidelines and patient outcomes (Grimshaw & Russell, 1993; Johnston *et al*., 1994; Lobach & Hammond, 1994; Tierney *et al*., 1995). Development of guideline-based CDSSs has thus been proposed as a strategy to promote the implementation of guidelines (Field & Lohr, 1992; McDonald & Overhage, 1994). In the past two decades, a number of guideline modelling methods and tools have been developed for the purpose of developing guideline-based CDSSs. Among them, some typical guideline modelling tools are summarized in Table 2 in terms of 'representation schemes', 'inference mechanisms' and 'limitations in uncertainty handling' aspects.

From the summary of guideline modelling tools listed in Table 2, it can be seen that the advantages of these tools are that they are specifically targeted at representing and reasoning about clinical guidelines. In some modelling tools such as Asbru and GLARE, uncertainties in temporal scopes during the process of diagnosis have been taken into consideration, and in both GLARE and PROforma uncertainties in drawing diagnosis conclusions with the same clinical symptoms based on different types of medical domain knowledge have also been considered. However, uncertainties in medical domain knowledge contained in clinical guidelines have not been sufficiently dealt with in these modelling tools' representation schemes, and the modelling tools' inference mechanisms have not taken into consideration all uncertainties in clinical symptoms.

As shown in Table 2, there is difficulty in tackling uncertainties in either medical domain

Table 2: *Representation schemes, inference mechanisms and limitations in uncertainty handling of typical guideline modelling tools*

Guideline modelling tools	*Representation schemes*	*Inference mechanisms*	*Limitations in uncertainty handling*
Arden (Starren *et al*., 1994)	Rules	Rules chaining	Lack of support for handling uncertainties in both medical domain knowledge and clinical symptoms
Asbru (Miksch *et al*., 1998)	Time-oriented skeletal plans	Task-specific reasoning	Flexible in representing uncertainty in temporal scopes by bounding intervals, but lack of support for handling more uncertainties in both medical domain knowledge and clinical symptoms
EON (Tu & Musen, 1999)	Frames	Temporal reasoning	Lack of support for handling uncertainties in both medical domain knowledge and clinical symptoms
GASTON (de Clercq *et al*., 2001)	Frames	Temporal reasoning	Lack of support for handling uncertainties in both medical domain knowledge and clinical symptoms
GLARE (Terenziani *et al*., 2001)	Actions	Temporal reasoning and hypothetical reasoning	Having the capability of representing and reasoning with temporal uncertainties, and comparing alternative paths in a guideline using hypothetical reasoning facility, but lack of support for handling uncertainties in clinical symptoms and medical domain knowledge which are used to generate diagnostic or therapeutic hypotheses
GLIF (Peleg *et al*., 2000)	Frames	Temporal reasoning	Lack of support for handling uncertainties in both medical domain knowledge and clinical symptoms
GUIDE (Quaglini *et al*., 2001)	Petri nets	Temporal reasoning	Lack of support for handling uncertainties in both medical domain knowledge and clinical symptoms
PROforma (Fox *et al*., 1998)	Task-based formalism	Task-specific reasoning	Using rules to establish a preference order on the decision options and letting clinicians choose alternative options, but lack of support for handling uncertainties in medical domain knowledge used to construct those rules

knowledge or clinical symptoms for these guideline modelling tools. Uncertainty handling is a weakness in most guideline-based CDSSs, and how to overcome the weakness in modelling guidelines is a critical issue in the CDSS research area. Kong *et al*. (2008) proposed that one potential way of overcoming the difficulties in uncertainty handling in the CDSS research area is to explore the potential offered by the latest development in decision sciences, especially the branch of decision making under uncertainty. In this paper, the recently developed belief rule-base (BRB) inference methodology based on evidential reasoning (ER) approach (RIMER) (Yang *et al*., 2006) in the decision science area is outlined in Section 2, and how to use the BRB and ER approach (Yang & Sen, 1994; Yang & Singh, 1994; Yang, 2001; Yang & Xu, 2002) employed in RIMER to model medical domain knowledge and the inference process contained in clinical guidelines is explored in Section 3. The advantages of employing RIMER to develop a CDSS are demonstrated by a case study in Section 4. Finally, concluding remarks about the study and possible future research directions in this area are discussed in Section 5.

2. Outline of RIMER

RIMER is proposed for modelling a hybrid rule base using a belief structure and for inference in the rule-based system using the ER approach. In the methodology, knowledge is represented by a new knowledge representation scheme, belief rules, which are different from conventional

rules in that they are designed with belief degrees embedded in all possible consequents of a rule, and other knowledge representation parameters such as the weights of both attributes and rules are also considered in this scheme. Such a BRB is capable of capturing vagueness, incompleteness and non-linear causal relationships in knowledge.

In an established BRB, an input to an antecedent attribute is transformed into a belief distribution on referential values. Subsequently, inference in a BRB is implemented using the ER approach. As a result, the possible consequents in the inferred result are also associated with belief degrees. If it is difficult to tell the severity difference between two patients' illness with all possible diagnosis consequents associated with belief degrees, the concept of expected utility and utility interval (Yang & Xu, 2002), which means severity score and severity interval in a belief rule-based CDSS, can be used to generate numerical values to rank the seriousness of different patients' illness caused by the same disease. What follows is a brief introduction to the BRB model for representing medical domain knowledge, rule inference using the ER approach and optimal learning methods for training BRBs in RIMER.

2.1. *BRBs for representing medical domain knowledge*

BRBs are extended from traditional rule bases by adding a belief structure, in which knowledge representation parameters including rule weights, attribute weights and belief degrees in consequents are embedded.

Conventionally, in a rule base, the kth rule R_k in an IF–THEN format can be described as

$$\text{If } A_1^k \wedge A_2^k \wedge \cdots \wedge A_{T_k}^k, \text{ then } D_k \qquad (1)$$

where $A_i^k (i = 1, \ldots, T_k)$ is a referential value of the ith antecedent attribute in the kth rule and T_k is the number of antecedent attributes used in the kth rule. D_k is the consequent of the kth rule.

If rule weights, attribute weights and all possible consequents associated with belief degrees are taken into account, rule (1) can be extended to a packet rule using a belief structure, which is referred to as a belief rule R_k and can be described as follows:

$$\text{If } A_1^k \wedge A_2^k \wedge \cdots \wedge A_{T_k}^k,$$

then

$$\{(D_1, \bar{\beta}_{1k}), (D_2, \bar{\beta}_{2k}), \ldots, (D_N, \bar{\beta}_{Nk})\} \qquad \bar{\beta}_{ik} \geq 0, \sum_{i=1}^{N} \bar{\beta}_{ik} \leq 1 \qquad (2)$$

with a rule weight θ_k and attribute weights

$$\delta_{k1}, \delta_{k2}, \ldots, \delta_{kT_k}, k \in \{1, \ldots, L\}$$

where $\bar{\beta}_{ik} (i \in \{1, \ldots, N\})$ is the belief degree given by experts to which D_i is believed to be the consequent if in the kth belief rule the input satisfies the packet antecedents $A^k = (A_1^k, A_2^k, \ldots, A_{T_k}^k)$, the attribute weight δ_{ki} $(i = 1, \ldots, T_k;\ k = 1, \ldots, L)$ represents the relative importance of the ith antecedent attribute in the kth rule, and the rule weight θ_k represents the relative importance of the kth rule in the rule base. L is the number of belief rules in the rule base. T_k is the number of antecedent attributes used in the kth belief rule. N is the number of all possible consequents in the rule base.

A BRB is a collection of belief rules. It is not difficult to see the difference between a traditional IF–THEN rule and a belief IF–THEN rule. In a traditional rule, the consequent is either 100% true or 100% false. Such a rule base has limited capacity in representing knowledge in the real world. For example, it is incapable of capturing a continuous causal relationship between antecedents and consequents. Take for example the rule 'IF electrocardiogram (ECG) consistent with myocardial ischaemia THEN high clinical probability of myocardial damage'. From the rule, the causal relationship between the antecedent attribute 'ECG consistent with myocardial ischaemia' and the consequent attribute 'high clinical probability of myocardial damage' is of 100% certainty. But in real-life diagnosis, a doctor may not judge one patient's ECG to be 100% consistent with myocardial ischaemia, and he/she may describe his/her judgement as 'ECG is strongly

consistent with myocardial ischaemia', 'ECG is a little like myocardial ischaemia', 'ECG looks like myocardial ischaemia with 50% probability' and so on, so that the probability of myocardial damage for the patient can be high, moderate or low with different degrees of certainty. This means that there is actually a continuous causal relationship between the antecedent attribute 'ECG consistent with myocardial ischaemia' and the consequent attribute 'clinical probability of myocardial damage'. However, a traditional IF–THEN rule is not capable of handling this kind of relationship between antecedents and consequents. The belief structure of a BRB provides better flexibility in representing knowledge of different structures and complexity, such as continuous and uncertain relationships between antecedents and consequents (Xu *et al.*, 2007). If the above rule is extended with a belief structure, a belief rule can be established in natural language like 'IF ECG is strongly consistent with myocardial ischaemia THEN high clinical risk of myocardial damage with a probability of 80%'.

2.2. Rule inference using the ER approach

The ER approach is proposed for dealing with multiple attribute decision analysis (MADA) problems having both quantitative and qualitative attributes with uncertainties. Different from traditional MADA approaches that describe a MADA problem using a decision matrix, the ER approach uses the belief decision matrix, in which each alternative on an attribute is assessed by a distribution using a belief structure.

When the ER approach is applied to reason with a BRB, the packet antecedent A^k ($k=1, \ldots, L$) of a belief rule can be considered as a basic attribute with an attribute weight ω_k ($k=1, \ldots, L$), which is assessed to a consequent D_i ($i=1, \ldots, N$) with a belief degree β_{ik} ($i=1, \ldots, N$; $k=1, \ldots, L$), where N is the number of possible consequents in the BRB and L is the number of rules in the BRB. A BRB described by a belief rule expression matrix is shown in Table 3.

In the matrix, ω_k ($k=1, \ldots, L$) is the activation weight of the kth rule, which measures the degree to which the kth rule is activated and weighted. β_{ik} is the belief degree to which D_i is the consequent if the input satisfies the packet antecedent A^k in the kth rule for $i=1, \ldots, N$, $k=1, \ldots, L$.

Table 3: *Belief rule expression matrix for a BRB*

	Input				
Output	$A^1(\omega_1)$	$A^2(\omega_2)$	$\cdots$ $A^k(\omega_k)$	$\cdots$	$A^L(\omega_L)$
D_1	β_{11}	β_{12}	$\cdots$ β_{1k}	$\cdots$	β_{1L}
D_2	β_{21}	β_{22}	$\cdots$ β_{2k}	$\cdots$	β_{2L}
$\vdots$	$\vdots$	$\vdots$	$\cdots$ $\vdots$	$\cdots$	$\vdots$
D_i	β_{i1}	β_{i2}	$\cdots$ β_{ik}	$\cdots$	β_{iL}
$\vdots$	$\vdots$	$\vdots$	$\cdots$ $\vdots$	$\cdots$	$\vdots$
D_N	β_{N1}	β_{N2}	$\cdots$ β_{Nk}	$\cdots$	β_{NL}

Source: Yang *et al.* (2006).

Given an input $U=(U_i, i=1, \ldots, T)$ together with its corresponding belief degree $\varepsilon=(\varepsilon_i, i=1, \ldots, T)$, where T is the total number of antecedent attributes in the rule base, U_i ($i=1, \ldots, T$) is the input value of the ith antecedent attribute, and ε_i ($i=1, \ldots, T$) represents the degree of belief assigned to the input value U_i of the ith antecedent attribute, which reflects the uncertainty of the input data, how should the BRB be used to infer and generate output? Before an inference process starts, all input data need to be transformed to a distribution on referential values of each antecedent attribute using belief degrees, and this transformation process can be implemented by rule or utility-based equivalence transformation techniques (Yang, 2001). For example, the input value U_i for the ith antecedent attribute along with its belief degree ε_i can be transformed as

$$S(U_i, \varepsilon_i)=\{(A_{ij}, \alpha_{ij}); j=1, \ldots, J_i\} \quad i=1, \ldots, T \qquad (3)$$

where A_{ij} is the jth referential value of the ith antecedent attribute, α_{ij} is the degree to which the input U_i with belief degree ε_i belongs to the referential value A_{ij} with $\alpha_{ij} \geq 0$ and $\sum_{j=1}^{J_i} \alpha_{ij} \leq 1$ ($i=1, 2, \ldots, T$), and J_i is the number of all referential values of the ith antecedent attribute.

After the input transformation, the activation weight ω_k ($k=1, \ldots, L$), which measures the degree to which the packet antecedent A^k in the kth rule is activated, can be calculated by (Yang *et al*., 2006)

$$\omega_k = \frac{\theta_k \alpha_k}{\sum_{j=1}^{L} \theta_j \alpha_j} = \frac{\theta_k \prod_{i=1}^{T_k} (\alpha_i^k)^{\bar{\delta}_{ki}}}{\sum_{j=1}^{L} \left[\theta_j \prod_{l=1}^{T_k} (\alpha_l^j)^{\bar{\delta}_{jl}}\right]} \quad k=1, \ldots, L \tag{4}$$

where

$$\bar{\delta}_{ki} = \frac{\delta_{ki}}{\max\limits_{i=1,\ldots,T_k}\{\delta_{ki}\}} \quad 0 \le \bar{\delta}_{ki} \le 1$$

is transformed from antecedent weight δ_{ki} ($i=1, \ldots, T_k$; $k=1, \ldots, L$) representing the relative importance of the ith antecedent attribute in the kth rule. θ_k ($k=1, \ldots, L$) is the relative weight of the kth rule. α_i^k ($i=1, \ldots, T_k$)is the individual matching degree to which the input U_i ($i=1, \ldots, T_k$) belongs to A_i^k ($i=1, \ldots, T_k$; $k=1, \ldots, L$) that is the referential value of the ith antecedent attribute used in the kth rule, and it is generated from the input transformation as described in (3), with $\alpha_i^k \ge 0$ and $\sum_{i=1}^{T_k} \alpha_i^k \le 1$. $\alpha_k = \prod_{i=1}^{T_k} (\alpha_i^k)^{\bar{\delta}_{ki}} (k=1, \ldots, L)$ is called the combined matching degree to which the input vector U matches the packet antecedent A^k in the kth rule. T_k is the total number of antecedents in the kth belief rule. L is the total number of all belief rules in the BRB.

It can easily be found from (4) that, in the calculation of the combined matching degree α_k ($k=1, \ldots, L$) of input to packet antecedent, all individual matching degrees α_i^k ($i=1, \ldots, T_k$; $k=1, \ldots, L$) and all antecedent weights δ_{ki} ($i=1, \ldots, T_k$; $k=1, \ldots, L$) have been taken into account, and then the calculation of the activation weight ω_k ($k=1, \ldots, L$) takes into consideration both rule weights θ_k ($k=1, \ldots, L$) and the calculated combined matching degrees of input to packet antecedent. This means that all knowledge representation parameters play their roles in calculating a rule's activation weight.

As to the belief degree $\bar{\beta}_{ik}$ ($0 \le \sum_{i=1}^{N} \bar{\beta}_{ik} \le 1; i=1, \ldots, N; k=1, \ldots, L$) originally given by experts when a BRB represented by (2) is established, if $\sum_{i=1}^{N} \bar{\beta}_{ik} = 1$ the kth belief rule is said to be complete; otherwise, it is incomplete. If $\sum_{i=1}^{N} \bar{\beta}_{ik} = 0$, it means the output of the kth belief rule is completely unknown. The incompleteness of the consequent in a rule when the rule is established is caused by lack of domain knowledge or expert experience. The incompleteness of a rule can also be caused by its antecedents due to lack of data. For instance, if the input for the antecedent attributes of a rule is completely unknown, a completely unknown consequent will be generated. If the input of antecedent attributes is partially known, the consequent of the rule will also be partially known or incomplete. In the inference process, such incompleteness of rules caused by input data should also be taken into consideration, because an incomplete input for an antecedent attribute will cause an incomplete output or consequent in each of the rules in which the attribute plays its antecedent role. For this reason, belief degrees in consequents of a rule should take into account not only original domain knowledge extracted from experts but also real input data which may cause incompleteness in consequents as well. The original belief degree $\bar{\beta}_{ik}$ ($0 \le \bar{\beta}_{ik} \le 1; \sum_{i=1}^{N} \bar{\beta}_{ik} \le 1$) given to the ith possible consequent D_i ($i=1, \ldots, N$) in the kth rule which is extracted from experts when a BRB is established should be updated on the basis of the actual input information in the inference process by (Yang *et al*., 2006)

$$\beta_{ik} = \bar{\beta}_{ik} \frac{\sum_{t=1}^{T_k} \left[\tau(t,k) \sum_{j=1}^{J_t} \alpha_{tj}\right]}{\sum_{t=1}^{T_k} \tau(t,k)} \quad (i=1, \ldots, N; k=1, \ldots, L; t=1, \ldots, T_k) \tag{5}$$

where β_{ik} is the belief degree in consequent D_i when the kth rule is activated by the actual input

and it is determined by the original belief degree $\bar{\beta}_{ik}$ together with the incompleteness of real input data, in which

$$\tau(t,k)=\begin{cases}1 & \text{if the } t\text{th antecedent attribute is}\\ & \text{used in defining } R_k\ (t=1,\ \ldots,\ T_k)\\ 0 & \text{otherwise}\end{cases}$$

and α_{ij} is the degree to which the input U^k belongs to the referential value A_{tj} ($t=1,\ \ldots,\ T_k$; $j=1,\ \ldots,\ J_t$) with $\alpha_{tj}\geq 0$ and $\sum_{j=1}^{J_t}\alpha_{tj}\leq 1$ ($j=1,\ \ldots,\ J_t$), and the transformation from input U^k to A_{tj} is described as in (3), where A_{tj} is the jth referential value of the tth antecedent attribute and R_k is the kth rule in the BRB. N is the number of consequents in the kth rule. T_k is the number of antecedents in the kth rule, and J_t is the number of referential values of the tth antecedent attribute in the kth rule.

After the activation weight of each rule and belief degrees in the possible consequents of each rule in a BRB have been determined, the ER algorithm (Yang & Xu, 2002) can be applied directly to aggregate all activated rules in a BRB to generate the combined degrees of belief in the consequents of a BRB as follows:

$$O(U)=\{(D_j,\ \beta_j),\ j=1,\ \ldots,\ N\} \qquad (6)$$

which means that, given an input to a belief rule-based system in the vector form $U=\{U_i,\ i=1,\ \ldots,\ T\}$, the outcome is consequent D_j with a belief degree β_j ($j=1,\ \ldots,\ N$).

Finally, if necessary the expected utility and utility interval of distributed diagnosis consequents which are used to measure severity of diseases in the context of clinical decision making can be calculated so that the seriousness of patients' illness can be ranked. The details of the concept and calculation of the expected utility and utility interval of the ER approach can be found in Yang and Xu (2002).

2.3. *Optimal learning methods for training BRBs in RIMER*

In an established BRB, although it is possible that knowledge representation parameters such as belief degrees, rule weights and attribute weights together with other domain knowledge can be extracted from experts, it is difficult to accurately determine the parameters entirely subjectively. A change in the parameters may lead to changes in the performance of a belief rule-based system.

Yang *et al.* (2007) proposed that the parameters of a BRB can be trained using optimization models. An illustration of an optimal learning process is shown in Figure 1. In the figure, U is a given input, $\hat{O}$ the corresponding observed output whether measured using instruments or assessed by experts, O the simulated output generated by the belief rule-based system, $\xi(P)$ the difference between $\hat{O}$ and O, and P the vector of training parameters including belief degrees in consequents β_{ik} ($i=1,\ \ldots,\ N$; $k=1,\ \ldots,\ L$), rule weight θ_k ($k=1,\ \ldots,\ L$) and antecedent weight δ_{kj} ($k=1,\ \ldots,\ L$; $j=1,\ \ldots,\ T_k$). The objective of the training is to minimize the difference $\xi(P)$ by adjusting the parameters including β_{ik}, θ_k and δ_{kj}. Different optimal training problems can be formulated depending on different types of input and output of the belief rule-based system, and some existing optimization tools and algorithms can be applied to solve these problems. Yang *et al.* (2007) constructed three kinds of optimal learning models based on the nature of a belief rule-based system's output, which can be numerical, subjective or in both numerical and subjective formats; the FMINCON function in Matlab, which is used to find the minimum of a constrained non-linear multivariable function, was used in their study to solve the single-objective model. Chang *et al.* (2009) also proposed an algorithm based on the gradient and dichotomy methods to train knowledge representation parameters in BRBs.

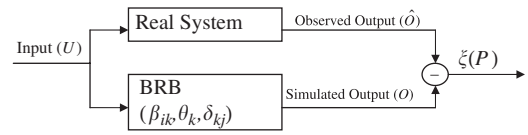

Figure 1: *Illustration of optimal learning process (Source: Yang et al., 2007).*

3. Use BRB and ER to develop a guideline-based CDSS

CDSSs are large systems consisting of interrelated components working together in a complex manner. Typically, a CDSS should consist of three different kinds of components: a knowledge base, which contains the rules necessary for the completion of deriving diagnostic or therapeutic decisions; a database, in which data and conclusions can be stored; and an inference mechanism, which matches rules to data to derive its clinical conclusions. The focus of this paper is on building an appropriate 'knowledge base' and 'inference mechanism' so as to provide intelligent and accurate clinical decision support in target clinical areas.

The first step in developing such a CDSS is to model target clinical guidelines by a BRB as represented by (2), in which antecedent attributes of rules are clinical symptoms or some diagnosis decisions already made by doctors or some other belief rules in the BRB and corresponding consequent attributes are possible diagnostic or therapeutic decisions. Knowledge representation parameters which consist of rule weights, attribute weights and belief degrees in consequents in a BRB are extracted from domain experts, and can also be trained by real clinical data through different optimal learning methods as described in Section 2.3. If there is no uncertainty in both antecedent and consequent attributes, and there is no need to combine different rules to make a clinical decision, a BRB would reduce to a traditional rule base.

After the establishment of the knowledge base with belief rules, the inference mechanism of the CDSS can be built by modelling the diagnosis process using the ER approach. The belief rule-based inference process in a CDSS using the ER approach can be described by the following six steps.

Step 1: Set rules together with knowledge representation parameters including rule weights, attributes weights and belief degrees in consequents which can be extracted from clinical domain experts.

Step 2: Transform input clinical data to a distribution on referential values of relevant antecedent symptoms using belief degrees as shown in (3).

Step 3: Calculate the activation weight of each rule in the BRB using (4).

Step 4: Update belief degrees to possible consequents in the BRB based on the input information using (5).

Step 5: Aggregate all activated rules using the ER approach to generate a combined belief degree in possible consequents as described by (6).

Step 6: (optional) If necessary, calculate expected severity and severity interval of different diagnostic consequents to rank the seriousness of patients' illness caused by the same disease. For example, if the severity score of H clinical risk is set to be 1, M clinical risk set to be 0.5 and L clinical risk set to be 0, a patient's overall severity score would be 0.8 if he/she is assessed as H clinical risk with 60% probability and M clinical risk with 40% probability.

For a better understanding, a flowchart as shown in Figure 2 can be used to illustrate the whole inference process using the ER approach in the CDSS.

The next section describes how to model part of an exemplary guideline for clinical risk assessment by BRB and inference with the ER approach in a CDSS, and a simulated patient's data are used to validate the methodology.

4. A case study

4.1. Guideline description

The clinical decision support guideline 2003-05 for 'Acute Upper Gastrointestinal (GI) Bleed' (Central Manchester and Manchester Children's University Hospitals NHS Trust, 2003) in the Emergency Department was selected as the target clinical guideline, and the clinical risk assessment part of the guideline was used for the case study. The guideline has been developed by clinicians. It was originally published on Central

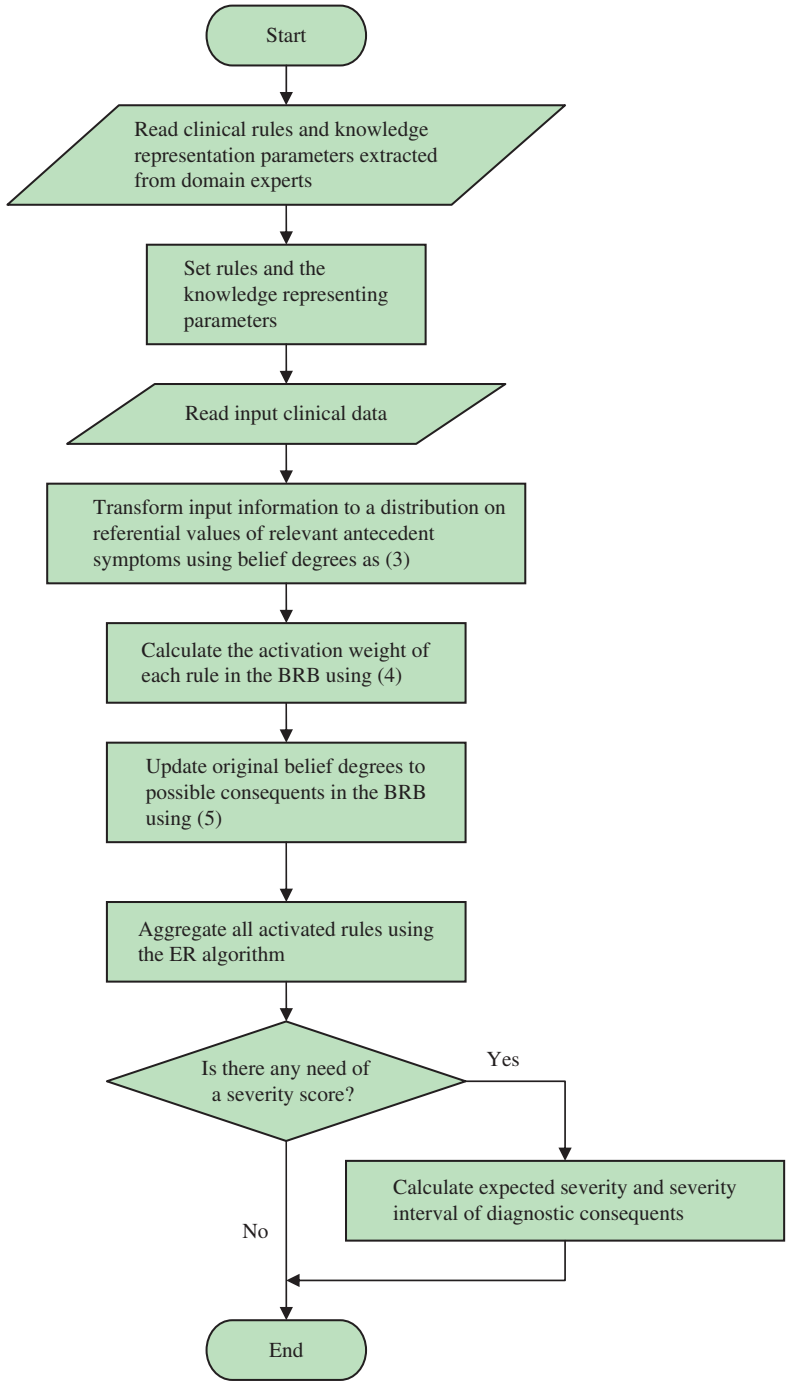

Figure 2: *Inference process in a CDSS using the ER approach.*

Manchester and Manchester Children's University Hospitals NHS Trust Intranet (UK) in 2003, and then its content was reviewed by the Clinical Effectiveness Committee of the British Association for Emergency Medicine in January 2005.

4.2. Domain knowledge modelling in the BRB

The guideline is designed by clinicians. When the medical knowledge it contains is transformed into sets of traditional rules, it seems that there is no uncertainty in the rules. However, in real-life clinical environments, there could be uncertainties in both clinical signs and symptoms and clinical domain knowledge. Most uncertainties would appear in describing clinical symptoms and deriving diagnosis conclusions. For example, conditions in one rule may not always be met with 100% accuracy. Even if two patients are diagnosed as having the same disease, the seriousness of their illness may be different. Accordingly, the two patients may be treated in a different time order. Furthermore, due to differences in domain knowledge and practice experience, diagnosis conclusions from different clinicians about the same clinical symptoms may not always be the same. In such situations, belief rules may provide an alternative solution to accommodate different types and degrees of uncertainty in representing both clinical data and clinical domain knowledge.

A BRB as shown in Table 4 for assessing the clinical risk of patients with acute upper GI bleed can be established to do the assessment more accurately. In Table 4, R^{u} represents the clinical risk of acute upper GI bleed, and F^{u}_{i} ($i = 1, \ldots, 10$) represents clinical symptoms or diagnoses related to acute upper GI bleed, where F^{u}_{1} stands for known or suspected oesophageal varices, F^{u}_{2} for pulse > 130 bpm, F^{u}_{3} for systolic blood pressure (SBP) < 90 mmHg, F^{u}_{4} for postural SBP drop > 20 mmHg, F^{u}_{5} for 'on non-steroidal anti-inflammatory drugs or anticoagulants', F^{u}_{6} for major co-morbidity (e.g. cardiac or renal impairment), F^{u}_{7} for stigmata of liver disease, F^{u}_{8} for 'witnessed acute fresh red blood in vomit', F^{u}_{9} for over 75 years old, and F^{u}_{10} for urea > 8. H, M and L stand for high, moderate and low clinical risk respectively. Y and N stand for 'yes' and 'no'.

In the BRB shown in Table 4, each rule has only one consequent with a belief degree of exactly 1 and all rule weights and attribute weights are assumed to be 1. This means that there is no uncertainty in the knowledge of using these signs and symptoms to assess the clinical risk of acute upper GI bleed. If there is no uncertainty in clinical symptoms, the above BRB would reduce to a traditional rule base. However, uncertainties are unavoidable in clinical signs and symptoms, and in this situation the BRB can provide a more pertinent relationship between antecedent symptoms and clinical

Table 4: *BRB for clinical risk assessment of acute upper GI bleed*

No.	*W*	*Antecedent*	*Consequent*
1	1	(F^{u}_{1} is Y)	R^{u} is {(H, 1)}
2	1	(F^{u}_{2} is Y)	R^{u} is {(H, 1)}
3	1	(F^{u}_{3} is Y)	R^{u} is {(H, 1)}
4	1	(F^{u}_{4} is Y)	R^{u} is {(H, 1)}
5	1	(F^{u}_{1} is N $\wedge$ F^{u}_{2} is N $\wedge$ F^{u}_{3} is N $\wedge$ F^{u}_{4} is N $\wedge$ F^{u}_{5} is Y)	R^{u} is {(M, 1)}
6	1	(F^{u}_{1} is N $\wedge$ F^{u}_{2} is N $\wedge$ F^{u}_{3} is N $\wedge$ F^{u}_{4} is N $\wedge$ F^{u}_{6} is Y)	R^{u} is {(M, 1)}
7	1	(F^{u}_{1} is N $\wedge$ F^{u}_{2} is N $\wedge$ F^{u}_{3} is N $\wedge$ F^{u}_{4} is N $\wedge$ F^{u}_{7} is Y)	R^{u} is {(M, 1)}
8	1	(F^{u}_{1} is N $\wedge$ F^{u}_{2} is N $\wedge$ F^{u}_{3} is N $\wedge$ F^{u}_{4} is N $\wedge$ F^{u}_{8} is Y)	R^{u} is {(M, 1)}
9	1	(F^{u}_{1} is N $\wedge$ F^{u}_{2} is N $\wedge$ F^{u}_{3} is N $\wedge$ F^{u}_{4} is N $\wedge$ F^{u}_{9} is Y)	R^{u} is {(M, 1)}
10	1	(F^{u}_{1} is N $\wedge$ F^{u}_{2} is N $\wedge$ F^{u}_{3} is N $\wedge$ F^{u}_{4} is N $\wedge$ F^{u}_{10} is Y)	R^{u} is {(M, 1)}
11	1	(F^{u}_{1} is N $\wedge$ F^{u}_{2} is N $\wedge$ F^{u}_{3} is N $\wedge$ F^{u}_{4} is N $\wedge$ F^{u}_{5} is N $\wedge$ F^{u}_{6} is N $\wedge$ F^{u}_{7} is N $\wedge$ F^{u}_{8} is N $\wedge$ F^{u}_{9} is N $\wedge$ F^{u}_{10} is N)	R^{u} is {(L, 1)}

risk of acute upper GI bleed than a traditional rule base.

4.3. Description of simulated clinical data

To validate the BRB established for clinical risk assessment in the 'Acute Upper GI Bleed' guideline together with its corresponding inference method, some real patient data are needed for testing the correctness of the rules and the reliability of the inference method. Because of the strict data protection regulations in the UK, we used simulated patient data to demonstrate the risk assessment process using the belief rule-based CDSS.

The clinical signs and symptoms of the simulated patient with acute upper GI bleed are given in Table 5.

4.4. Inference with BRB using the ER approach

Two methods of inference are often used in traditional rule-based CDSSs: forward and backward chaining (Shortliffe & Perreault, 1990). Inference with a BRB using the ER approach is similar to inference with a traditional rule base using the forward chaining method, which is a top-down method taking facts as they become available and attempting to draw conclusions from satisfied conditions in rules. The process of inference using forward chaining involves assigning values to attributes, evaluating conditions, and checking to see if all of the conditions in a rule are satisfied so as to fire satisfied rules. A general process of forward chaining is shown in Figure 3.

Table 5: *Simulated patient data for clinical risk assessment*

Disease	*Clinical signs and symptoms*
Upper GI bleed	Strongly suspected oesophageal varices Pulse is 131 bpm SBP is 90 mmHg Postural SBP drop is 20 mmHg Currently is on anticoagulants No major co-morbidity No stigmata of liver disease No fresh red blood in vomit 76 years old Urea is 8

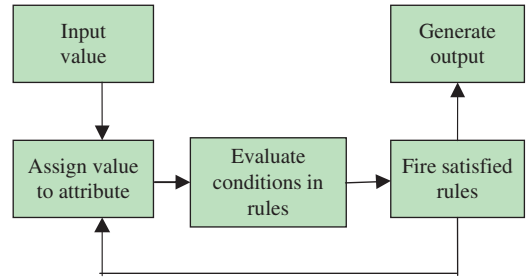

Figure 3: *A general process for forward chaining in a rule-based system.*

Inference with a BRB using the ER approach also involves assigning values to attributes, evaluating conditions and checking to see if all of the conditions in a rule are satisfied. However, inference with a BRB using the ER approach is different. First, value assignments in the ER approach are different from forward chaining due to the input transformation process. This is because there is a set of referential values for each antecedent attribute in each rule and the transformation process should determine the relationship between an input and each referential value in the antecedents of the rule. An input is assigned to each referential value in the antecedents with belief degrees. Second, the condition evaluation process is different. In the ER approach, since inputs can be transformed to distributed referential values, there may be conditions of more than one rule that can be satisfied. Third, conclusions are derived by an aggregation process. Using the ER approach, the conclusions generated by all the activated rules need to be aggregated to generate an overall conclusion, while in forward chaining there is no rule aggregation or combination process.

For clinical risk assessment of patients with acute upper GI bleed, F^{u}_{2}, F^{u}_{3}, F^{u}_{4}, F^{u}_{9} and F^{u}_{10} are quantitative clinical symptoms and their inputs are numerical values. For other clinical symptoms of a subjective nature, such as F^{u}_{1}, {known, strongly suspected, maybe, suspected with a low degree, no} can be used as its inputs, and {yes (Y), no (N)} can be used as inputs for

F^u_5, F^u_6, F^u_7 and F^u_8. Since the BRB for clinical risk assessment and its knowledge representation parameters has been set as shown in Table 4, the next step as described in Section 3 should be transforming input clinical data of the patient to distributed referential values of antecedent symptoms using belief degrees.

4.4.1. Input transformation In this study, {Y, N} is used as a set of referential values for all clinical symptoms. The distributed values transformed from the original input data as provided in Table 5 are as follows: F^u_1, {(Y, 0.8), (N, 0.2)}; F^u_2, {(Y, 0.67), (N, 0.33)}; F^u_3, {(Y, 0.5), (N, 0.5)}; F^u_4, {(Y, 0.5), (N, 0.5)}; F^u_5, {(Y, 1), (N, 0)}; F^u_6, {(Y, 0), (N, 1)}; F^u_7, {(Y, 0), (N, 1)}; F^u_8, {(Y, 0), (N, 1)}; F^u_9, {(Y, 0.6), (N, 0.4)}; F^u_{10}, {(Y, 0.5), (N, 0.5)}. In the above transformation process, a rule-based transformation method (Yang, 2001) is adopted for transforming both qualitative and quantitative input data.

(1) Qualitative input transformation. As to the qualitative input information regarding F^u_1, F^u_5, F^u_6, F^u_7 and F^u_8, Y and N are the set of referential values for all these clinical symptoms. Transformation rules should be set between the input options {known, strongly suspected, maybe, suspected with a low degree, no} and the referential values {Y, N} for transforming input information about F^u_1. In this paper, the following transformation rules are used for F^u_1: 'known' means 100% Y, 'strongly suspected' means 80% Y and 20% N, 'maybe' means 50% Y and 50% N, 'suspected with a low degree' means 20% Y and 80% N, and 'no' means 100% N. In real-life application, the options for acquiring original information about qualitative clinical symptoms should be set depending on the domain experts' knowledge and experience. There is no need to establish transformation rules for clinical symptoms of F^u_5, F^u_6, F^u_7 and F^u_8, because the referential values Y and N are options for acquiring original input. Based on the clinical data provided in Table 5, the transformed values for F^u_1, F^u_5, F^u_6, F^u_7 and F^u_8 are as follows: F^u_1, {(Y, 0.8), (N, 0.2)}; F^u_5, {(Y, 1), (N, 0)}; F^u_6, {(Y, 0), (N, 1)}; F^u_7, {(Y, 0), (N, 1)}; F^u_8, {(Y, 0), (N, 1)}.

(2) Quantitative input transformation. As to quantitative input data regarding F^u_2, F^u_3, F^u_4, F^u_9 and F^u_{10}, Y and N are also used as referential values for these symptoms, and each quantitative clinical symptom is associated with two kinds of threshold values defined by domain experts including an upper limit value and a lower limit value. Transformation rules for these quantitative clinical symptoms should include that, if the input is larger than the upper range value, the input can be transformed to 100% Y or N; if the input is lower than the lower range value, the input can be transformed to 100% N or Y; and if the input falls into the range between the lower and the upper limit values, the input can be transformed to

$$\{(\mathrm{Y}, \alpha_{\mathrm{Y}} = \frac{\textit{input value} - \text{lower range value}}{\text{upper range value} - \text{lower range value}} * 100\%),\ (\mathrm{N}, \alpha_{\mathrm{N}} = 1 - \alpha_{\mathrm{Y}})\}$$

or

$$\{(\mathrm{N}, \alpha_{\mathrm{N}} = \frac{\textit{input value} - \text{lower range value}}{\text{upper range value} - \text{lower range value}} * 100\%),\ (\mathrm{Y}, \alpha_{\mathrm{Y}} = 1 - \alpha_{\mathrm{N}})\}$$

where α_{Y} stands for the belief degree to which the input value can be transformed to Y and α_{N} stands for the belief degree to which the input value can be transformed to N.

The reason for us to adopt a saturated linear utility change process rather than a step utility change process in transforming original input numerical values of each quantitative clinical symptom to a set of referential values is that these rules can make the inference in the system better imitate human decision making in a real-life environment. Consider F^u_2 for example. If the input value of F^u_2 is larger than 130 bpm, then the patient will be at high risk based on the guideline. However, a question will arise as to what will be the judgement if the input value is exactly 130 bpm. In real-life clinical risk assessment for the diagnosis of patients with upper GI bleed, a clinician would make his assessment about a patient with a pulse of 130 bpm based on his experience and other observations instead

of using 130 as the only standard to make the judgement. To solve this problem in the belief rule-based CDSS, in this paper a value area of (127, 133) is used as an interval to define a gradual change area in risk assessment for the patient's pulse. Therefore, the input value for enquiry about F^{u}_2 equal to or higher than 133 bpm will be transformed to F^{u}_2: {(Y, 1), (N, 0)} and the input value for enquiry about F^{u}_2 equal to or lower than 127 bpm will be transformed to F^{u}_2: {(Y, 0), (N, 1)}. If the input value lies in the area (127, 133), it will be transformed to

$$F_2^u : \{(\mathrm{Y}, \alpha_\mathrm{Y} = \frac{\textit{input value} - 127}{133 - 127} * 100\%), (\mathrm{N}, \alpha_\mathrm{N} = 1\alpha_\mathrm{Y})\}$$

A similar transformation takes place in input information for enquiries about F^{u}_3, F^{u}_4, F^{u}_9 and F^{u}_{10}, and the linear change area is (85, 95) for F^{u}_3, (15, 25) for F^{u}_4, (70, 80) for F^{u}_9 and (5, 11) for F^{u}_{10}.

Based on the clinical data provided in Table 5, the transformed values for F^{u}_2, F^{u}_3, F^{u}_4, F^{u}_9 and F^{u}_{10} are

$$F_2^{\mathrm{u}}, \{(\mathrm{Y}, \alpha_Y = \frac{131\,(\textit{input value}) - 127\,(\text{lower range value})}{133\,(\text{upper range value}) - 127\,(\text{lower range value})} * 100\% = 0.67), (\mathrm{N}, \alpha_\mathrm{N} = 1 - \alpha_\mathrm{Y} = 0.33)\}$$

F^{u}_3, {(N, $\alpha_\mathrm{N} = (90 - 85)/(95 - 85) * 100\% = 0.5$), (Y, $\alpha_\mathrm{Y} = 1 - \alpha_\mathrm{Y} = 0.5$)}; F^{u}_4, {(Y, $\alpha_\mathrm{Y} = (20 - 15)/(25 - 15) * 100\% = 0.5$), (N, $\alpha_\mathrm{N} = 1 - \alpha_\mathrm{Y} = 0.5$)}; F^{u}_9, {(Y, $\alpha_\mathrm{Y} = (76 - 70)/(80 - 70) * 100\% = 0.6$), (N, $\alpha_\mathrm{N} = 1 - \alpha_\mathrm{Y} = 0.4$)}; and F^{u}_{10}, {(Y, $\alpha_\mathrm{Y} = (8 - 5)/(11 - 5) * 100\% = 0.5$), (N, $\alpha_\mathrm{N} = 1 - \alpha_\mathrm{Y} = 0.5$)}.

4.4.2. Rules' activation weights calculation
After the value assignment for antecedent symptoms, the next step is to calculate the activation weight for each packet antecedent in the rule base. Using

$$\alpha_k = \prod_{i=1}^{T_k} (\alpha_i^k)^{\bar{\delta}_{ki}} \quad k = 1, \ldots, L$$

as described in (4), the combined matching degrees of the input to each rule's packet antecedent are calculated as follows: $\alpha_1 = 0.8$, $\alpha_2 = 0.67$, $\alpha_3 = 0.5$, $\alpha_4 = 0.5$, $\alpha_5 = 0.0165$, $\alpha_6 = 0$, $\alpha_7 = 0$, $\alpha_8 = 0$, $\alpha_9 = 0.0099$, $\alpha_{10} = 0.0083$ and $\alpha_{11} = 0$. The activation weights ω_k ($k = 1, \ldots, 11$) for all rules are generated using $\omega_k = \theta_k \alpha_k / \sum_{j=1}^{L} \theta_j \alpha_j$ ($k = 1, \ldots, L$) as described in (4), as follows: $\omega_1 = 0.3194$, $\omega_2 = 0.2675$, $\omega_3 = 0.1996$, $\omega_4 = 0.1996$, $\omega_5 = 0.0066$, $\omega_6 = 0$, $\omega_7 = 0$, $\omega_8 = 0$, $\omega_9 = 0.004$, $\omega_{10} = 0.0031$ and $\omega_{11} = 0$.

4.4.3. Belief degrees update Next, belief degrees in the possible consequents of the activated rules in the rule base are updated, as shown in Table 4. Rules 1, 2, 3, 4, 5, 9 and 10 are activated according to the above activation weights ω_k ($k = 1, \ldots, 11$). After calculation of belief degrees in consequents using (5) based on the transformed input values described in Section 4.4.1, it is found that the updated belief degrees in possible consequents of the rules in the BRB as described in Table 4 remain as the original values because all the transformed inputs are complete. Here, a complete input means that, if the input U^k is transformed to the original distributed referential values with belief degrees as described in equation (3), $\sum_{j=1}^{J_i} \alpha_{ij}$ ($i = 1, \ldots, T_k$; $j = 1, \ldots, J_i$) should be 1. Consider F^{u}_1, for example; the sum of α_Y (0.8) and α_N (0.2) of F^{u}_1 transformed from the simulated input is 1, which means that the input to the antecedent symptom F^{u}_1 is also complete. If all antecedent attributes get complete inputs, the whole input is a complete one and the belief degrees in the consequents of the BRB remain the same as the original ones given by experts.

4.4.4. Rules aggregation via ER Finally, intelligent decision system (IDS) (Xu & Yang, 2005), a Windows-based multiple criteria assessment system which implements the ER approach, is used as a tool to aggregate all the activated rules. First, we should model the belief rule-based clinical risk assessment in the ER framework as an MADA problem by taking each patient's illness as an alternative to be assessed,

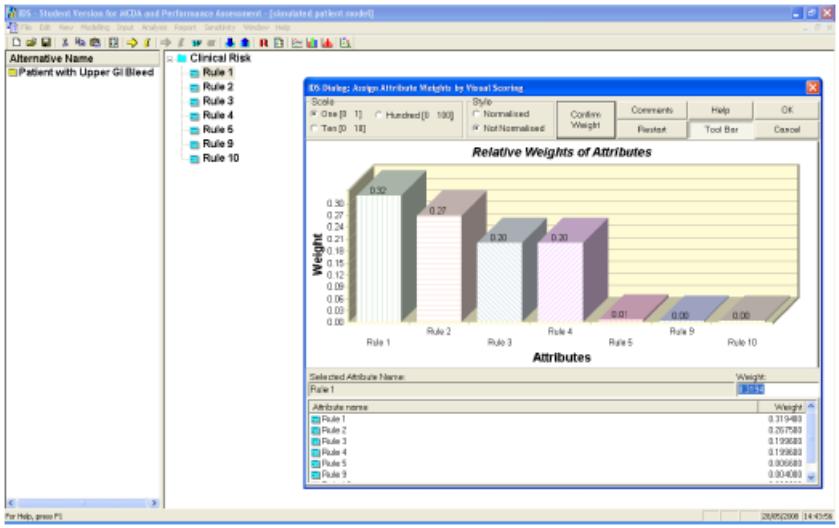

Figure 4: *Clinical risk assessment model in IDS.*

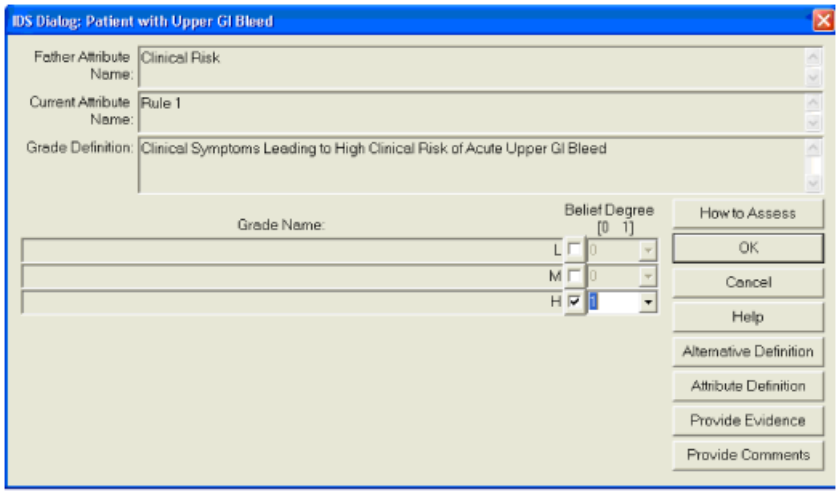

Figure 5: *IDS dialogue for acquiring belief degrees in consequents.*

taking clinical risk as the top attribute for the assessment of the patient's illness, and taking each activated rule's packet antecedent as a basic attribute for the assessment of the top attribute. In this model, each rule's activation weight acts like a basic attribute's weight, and each possible consequent of the BRB acts like each individual evaluation grade set for the basic attribute. Accordingly, belief degrees in possible consequents in the activated rules act like belief degrees to possible evaluation grades.

The model framed in IDS together with the inputs of the activated rules' activation weights is shown in Figure 4, in which the clinical risk assessment model of the simulated patient is shown on the upper left side and the dialogue box in IDS for acquiring each activated rule's weight is shown on the lower right side where each activated rule is treated as a basic attribute in the model. Accordingly, each activated rule's activation weight is treated as the relative weight of a basic attribute. A dialogue box in IDS for

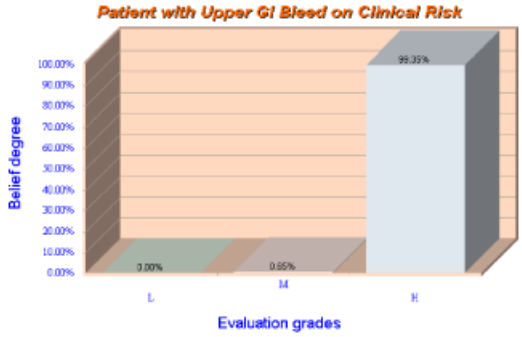

Figure 6: *Clinical risk assessment for simulated patient with upper GI bleed.*

acquiring belief degrees in the possible consequents of each activated rule for the clinical risk assessment model is shown in Figure 5.

After modelling, we can run IDS to generate assessments, and a final clinical risk assessment for the simulated patient with upper GI bleed is visually shown in Figure 6, which means the patient's clinical risk is assessed to be {(H, 0.9935), (M, 0.0065), (L, 0)} by IDS. If the severity score of H risk is set to 1, the severity score of M risk to 0.5 and the severity score of L risk to 0, the overall severity score of the simulated patient generated by the ER approach is 0.9968, and this score can be used to tell the seriousness difference between the patient's illness and other patients' illness which is also caused by upper GI bleed.

5. Concluding remarks

This paper describes how to employ a new belief rule inference methodology RIMER for developing a guideline-based CDSS, together with a case study to demonstrate its application. From the case study, the following conclusions can be drawn. First, RIMER can handle different types and degrees of uncertainties in both clinical domain knowledge and clinical data in a CDSS. Second, a belief rule-based CDSS can provide a distributed diagnostic recommendation which is more informative and comprehensive than other developed tools and systems. Third, if necessary, a seriousness score or seriousness interval can be calculated to rank the severity of patients' illness caused by the same disease.

However, further research and validation of the system are necessary by using real patient data. The original knowledge representation parameters should also be trained by real clinical data using the optimal learning methods introduced in Section 2, so that the belief rule-based CDSS is capable of learning and can automatically update its knowledge base.

In conclusion, employing RIMER for developing a guideline-based CDSS is a valid novel approach and real data can be used in future research.

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