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A NEW PATIENT TREATMENT DECISION SUPPORT SYSTEM FOR DIABETES

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Abstract. *Diabetes is not only mental suffering imposed on the patient's body, but also has high medical costs. Therefore, clinicians prescribing strategy must consider many factors. In this paper, we develop individualized diabetes drug recommendation system. The system uses fuzzy logic for individual differences in HbA1c levels of patients with different treatments. Using this system, hypoglycemic agents are recommended to the effective implementation of the ranking clinicians and drugs.*
Keywords: Patient-centered decision making, Fuzzy system, Type 2 diabetes mellitus, Domain ontology, Decision support system

1. **Introduction and Related Work.** According to the latest data released by the International Diabetes Federation [1], the number of diabetes patients worldwide has reached 415 million or one in 11 adults has diabetes. Without active intervention, the number of diabetes patients of worldwide will increase 55% to 642 million diabetes patients or one adult in 10 will have diabetes by 2040. In 2015, 5 million people died from diabetes-related diseases, or one death every 6 seconds. According to IDF estimates, 193 million diabetics have not been diagnosed, so there is a greater risk of complications. The cost of diabetes worldwide is now US $673 billion with 12% of global health expenditure dedicated to diabetes treatment and related complications. Notably, three quarters of people with diabetes live in low and middle income countries, so diabetes has exerted a tremendous impact on the socio-economic development of these nations.

In 2012, the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) jointly issued a statement on type 2 diabetes mellitus (T2DM) management [2,3]. They suggested that a clinical decision is based on patient-centered care. In view of the uncertainty inherent in the therapeutic type and sequence, this method is especially suitable for patients with T2DM. The statement recommended that setting of patient's personal glycemic targets is based on patient characteristics instead of the inflexible levels set by the ADA's "Standards of Medical Care in Diabetes 2011", which recommended lowering *HbA1c* to less than 7% for most patients [2].

Clinical practitioners thus need to select different drugs to meet the needs of patients. However, greater choice of clinical therapy may mean a lack of the long-term research into therapeutic effects needed to inform the decision makers, which implies uncertainty about the long-term benefits of new drugs. Vascular complications are a good example of the kinds of problems that can occur [4-6]. Ceriello et al. [7,8] based their investigation on the performance type of patients. First, they referred to the patient's major characteristics, including *HbA1c*, body mass index (BMI), occupational risk of hypoglycemia, chronic renal failure, weakening, and aging. Patients are divided into six groups, each of which has its own algorithm. By incorporating the glucose self-monitoring level, the study analyzed each patient's performance type. Finally, it provided patients with a gradual adjustment of glucose drugs. However, there has been no clinical evaluation of this study.

Ontologies are extremely important tools for the organization and representation of knowledge [9,10]. Chen et al. [11] proposed a diabetes medication recommendation system based on domain ontology. The system employed the knowledge base provided by a hospital specialist in Taichung's Department of Health and the database of the American association of clinical endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. The system builds ontology knowledge about the drugs' attributes and patients' symptoms, and then it uses Java Expert System Shell (JESS) to inference the most appropriate drugs. In 2014, Chen et al. [12] used domain ontology and rules reasoning to construct a clinical decision support system (CDSS) for undergoing surgery diabetic patients. By the clinical knowledge of experts, the system can be shared, updated, and reused through an ontology-based system. The system provides clinicians with evidence-based recommendations to promote medical quality.

Although growing numbers of researchers have considered the positive potential of CDSS, they did not consider patient's characteristics. For example, patient attitude, resources and support system lead to positive treatment strategies or *HbA1c* target. In addition, there are new anti-diabetic pharmaceutical options and new ideas to guide clinical doctors to prescribe prescription, such as new medicine SGLT2 and injection medicine GLP-1. In this paper, we adopted the 2015 guideline of the ADA and EASD published "A Patient-Centered Approach" of hyperglycemia in T2DM to build *HbA1c* target inference module and the Glucose-lowering agents ontology [1]. Furthermore, we propose a drug recommendation system for patients with T2DM.

The remainders of the paper are organized as follows. Section 2 describes the methods of drug recommendation system, which combines fuzzy logics and ontology reasoning. Section 3 shows result and discussion. Conclusions and future works are given in Section 4.

2. **Methods.**

The recommendation system of this plan consists of three modules: the patient consultation management module, the patient ideal *HbA1c* target inference module, and the Glucose-lowering agent ontology and reasoning module. The framework of the recommendation system is presented in Figure 1.

2.1. **Patient consultation management module.**

This module requires patients' personal data, which is also needed by the other modules. Sufficient communication between the clinical doctor and the patient is also necessary to evaluate seven factors of the ADA and EASD position statement [2]: (1) the risks associated with hypoglycemia and other drug adverse effects, (2) disease duration, (3) life expectancy, (4) important comorbidities, (5) established vascular complications, (6) patient attitude and expected treatment efforts, (7) resources and support system. Each of the seven factors is divided into five levels, ranging from integers 0 to 4. The clinical doctor also needs to record adverse drug reactions (ADRs) and history of diseases.

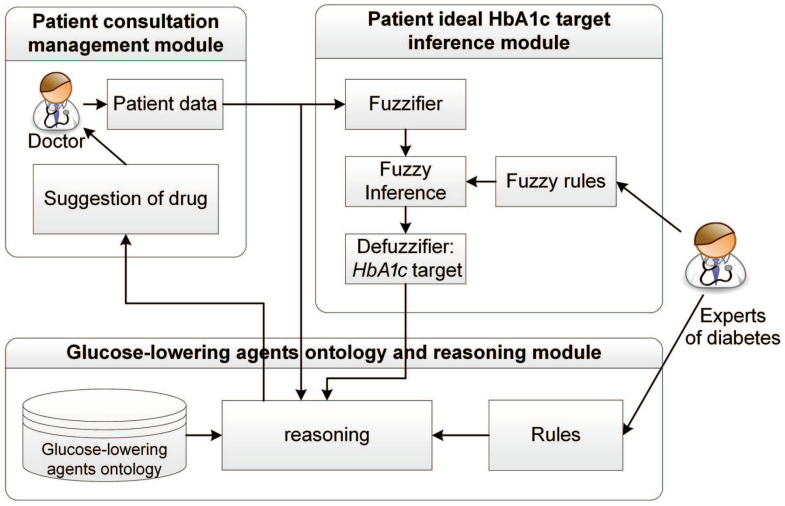

FIGURE 1. The recommendation system

TABLE 1. Names of membership functions, input and output variables

Variable	Name	Function1	Function2	Function3
$x1$	risks potentially associated with hypoglycemia and other drug adverse effects	Low	High	–
$x2$	disease duration	Newly Diagnosed	Long Standing	–
$x3$	life expectancy	Long	Short	–
$x4$	important comorbidities	Absent	Few/Mild	Severe
$x5$	established vascular complications	Absent	Few/Mild	Severe
$x6$	patient attitude and expected treatment efforts	Highly Motivated	Less Motivated	–
$x7$	resources and support system	Readily Available	Limited	–
z	*HbA1c*	More Stringent	Mild Stringent	Less Stringent

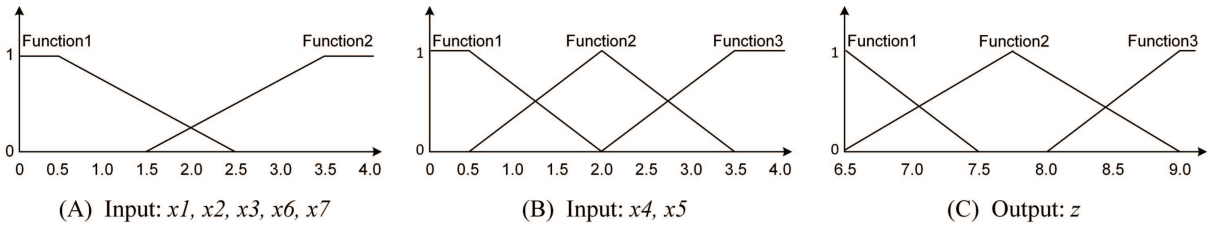

FIGURE 2. The membership functions of input and output variables

2.2. **Patient ideal *HbA1c* target inference module.** The main functional modules include fuzzifier, fuzzy rules, fuzzy inference, and defuzzifier. There are seven inputs, namely $x1, x2, \ldots, x7$, for fuzzy logic. The output value z is the ideal patient *HbA1c* target level, which takes individual differences into consideration. The names of the membership functions and input and output variables are shown in Table 1 and Figure 2.

The second step is to apply inputs to the fuzzy rules. The number of fuzzy rules depends on several input factors. For example, if the clinical doctor inputs $x1$, $x2$, $x4$ values, because the $x1$ has two membership functions (Low, High), the $x2$ has two membership

TABLE 2. Example of fuzzy rule table

Rule	$x1$	$x2$	$x4$	z
1	Low	Newly Diagnosed	Absent	More Stringent
2	Low	Newly Diagnosed	Few/Mild	Mild Stringent
3	Low	Newly Diagnosed	Severe	Less Stringent
4	Low	Long Standing	Absent	Less Stringent
5	Low	Long Standing	Few/Mild	Less Stringent
6	Low	Long Standing	Severe	Less Stringent
7	High	Newly Diagnosed	Absent	Less Stringent
8	High	Newly Diagnosed	Few/Mild	Less Stringent
9	High	Newly Diagnosed	Severe	Less Stringent
10	High	Long Standing	Absent	Less Stringent
11	High	Long Standing	Few/Mild	Less Stringent
12	High	Long Standing	Severe	Less Stringent

functions (Newly Diagnosed, Long Standing), and the $x4$ has three membership functions (Absent, Few/Mild, Severe), fuzzy rule will have 12 rules. Based on expert's experience and intuition, the fuzzy rule table is shown in Table 2. Rule 1 indicates that if $x1$ is low and $x2$ is newly diagnosed and $x4$ is absent, then z is more stringent. Rule 2 indicates that if $x1$ is low and $x2$ is newly diagnosed and $x4$ is few/mild, then z is mild stringent. Otherwise, the output z is less stringent in Rules 3-12, because $x1$ is high, or $x2$ is long standing, or $x4$ is severe.

2.3. **Glucose-lowering agents ontology and reasoning module.** We use Protégé with the Jess [13] plugin to implement the Glucose-lowering agents ontology and reasoning module. We create a Glucose-lowering agent ontology by the ADA and the EASD position statement [2]. The object properties in the ontology are shown Table 3.

This study developed Jess rules for reasoning are shown in Table 4, in which Glucose-lowering agents are not suitable for patients. The rules are described as follows.

Rule 1: If patients have a history of diseases which are related to the disadvantages of Glucose-lowering agents, then Glucose-lowering agents are not recommended.

Rule 2: If patients have ADRs, then the ADRs are not recommended.

TABLE 3. The object properties in the ontology

Object Property Name	Domain	Range
has_Advantages	Glucose-Lowering_Agents	Glucose-Lowering_Advantages
has_Cellular_mechanisms	Glucose-Lowering_Agents	Glucose-Lowering_Cellular_mechanisms
has_Compounds	Glucose-Lowering_Agents	Glucose-Lowering_Compounds
has_Cost	Glucose-Lowering_Agents	Glucose-Lowering_Cost
has_Disadvantages	Glucose-Lowering_Agents	Glucose-Lowering_Disadvantages
has_Primary_physiological_actions	Glucose-Lowering_Agents	Glucose-Lowering_Primary_physiological_actions
has_History_of_Diseases	Patients	Glucose-Lowering_Disadvantages
has_Adverse_Drug_Reactio-ns	Patients	Glucose-Lowering_Agents
Not_recommand	Patients	Glucose-Lowering_Agents

TABLE 4. Example of rules

No	Rule
1	Patients(?P) ∧ has_History_of_Diseases(?P, ?S1) ∧ Glucose-Lowering_Agents(?ND) ∧ has_Disadvantages(?ND, ?S2) ∧ sameAs(?S1, ?S2) → Not_recommand(?P, ?ND)
2	Patients(?P) ∧ has_Adverse_Drug_Reactions(?P, ?ND) → Not_recommand(?P, ?ND)

TABLE 5. Ten virtual patient's medical data

Patient ID	age	sex	$x1$	$x2$	$x3$	$x4$	$x5$	$x6$	$x7$	z ($HbA1c$)	has_History of Diseases	has_ADRs	Recommand GLDs
01	73	female	3	2	3	NaN	NaN	NaN	NaN	8.6	increasing_LDL-C, Edema	GLP-1	Biguanides, Sulfonylureas(SU), DPP-4, Insulins.
02	75	female	3	2	4	NaN	NaN	NaN	NaN	8.6	Heart_failure, increasing_LDL-C		Biguanides, Sulfonylureas(SU), DPP-4, GLP-1, Insulins.
03	64	female	2	1	2	NaN	NaN	NaN	NaN	6.9	Bone_fractures, increasing_LDL-C		Biguanides, Sulfonylureas(SU), DPP-4, GLP-1, Insulins.
04	76	female	4	3	3	2	1	NaN	NaN	8.8	increasing_LDL-C, Contraindications_CKD	DPP-4	Sulfonylureas(SU), GLP-1, Insulins.
05	61	female	4	3	2	3	2	NaN	NaN	8.6	Heart_failure, increasing_LDL-C, Contraindications_CKD, Weight_gain		DPP-4, GLP-1.
06	64	female	2	1	1	NaN	NaN	2	NaN	6.9			Biguanides, Sulfonylureas, TZDs, DPP-4, SGLT2, GLP-1, Insulins.
07	62	male	2	2	3	NaN	NaN	3	1	8.6	Gastrointestinal_side_effects_abdominal_cramping, increasing_LDL-C		Sulfonylureas, DPP-4, GLP-1, Insulins.
08	81	female	4	3	4	4	4	4	2	8.6	MI, increasing_LDL-C, Contraindications_CKD	DPP-4	Sulfonylureas, GLP-1, Insulins.
09	48	female	1	1	2	3	NaN	NaN	1	7.9	Patient_reluctance_about_injection, increasing_LDL-C		Biguanides, Sulfonylureas, DPP-4, GLP-1.
10	56	male	NaN	2	2	2	1	1	NaN	7.9	Weight_gain, increasing_LDL-C, Gastrointestinal_side_effects_nausea	TZDs	Biguanides, DPP-4.

When filtering out of not recommended Glucose-lowering drugs (GLDs), then the system can determine the other GLDs are recommended. For example, patient_01 has a history of "increasing LDL-C" and "Edema". TZDs have both disadvantages, "Bone fractures" and "Weight gain". One of SGLT2's disadvantages is "increasing LDL-C". By Rule 1, TZDs and SGLT2 will not be recommended for patient_01. Patient_01 also has ADRs with GLP-1. Thus, by Rule 2, GLP-1 will not be recommended to patient_01. This system provides seven common GLDs in Taiwan, which include "Biguanides, Sulfonylureas(SU), TZDs, DPP-4, SGLT2, GLP-1, Insulins". When TZDs, SGLT2 and GLP-1 are not recommended to patient_01, Biguanides, Sulfonylureas(SU), DPP-4, Insulins are recommended.

3. **Result and Discussion.** The diabetes diplomate created 10 virtual patient's medical data to evaluate decision support system (DSS). We use Mamdani-type fuzzy inference and mean of maximum (MeOM) to perform defuzzification. The virtual patient's medical data are shown in Table 5. The $x1, x2, x3, \ldots, x7$, has_History of Diseases and has_ADRs are input variables by diabetes diplomat; otherwise, the z is fuzzy inference output of *HbA1c* target and "Recommand GLDs" is output by ontology reasoning.

The diabetes diplomate evaluates 8-question, 5-point survey, in terms of perceived usefulness, satisfaction degree, and behavioral intentions to use. All the scores were expressed as a percentage. The feedback given by the clinicians will be used for the maintenance of the ontology and the prototype. With regard to measuring the satisfaction of the system, diabetes diplomate like using the DSS and the system is recommended. That indicated the DSS has good performance and effectiveness both in 80%. The system also performs 80% for accurate, which can assist clinicians in the management of diabetes mellitus during selecting drugs. Thus, the participants did not have complete confidence to continue to use this system at work. As a result, only 60% of clinicians will use this system in the future and will recommend to others. It must be emphasized that the DSS is not created to replace human clinical decision-making.

4. **Conclusions.** The number of patients with diabetes is increasing. Diabetes imposes psychological, physical, and financial hardship on patients. Thus, the prescription strategy of clinical doctors must consider many factors. To address this, we developed an individualized drug recommendation system for patients with diabetes, which combines fuzzy logic and ontology reasoning. It promotes the new concept of "patient-centered diabetes therapy". In addition to aiding doctors' clinical diagnosis, the system not only can serve as a guide for specialty doctors, but also can help non-specialty doctors and young doctors with their drug prescriptions. Based on the feedback system of operations, for example, the weight of seven factors can be dynamic to setting. We will improve our system interface and dynamic weighting calculations in the near future.

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