Evaluating New Drugs by Fuzzy Inference System

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Abstract

Knowledge of medicinal chemical compounds is complex and evidence-based. In this paper, knowledge of drugs was extracted from experts, and evaluated with sophisticated computation techniques to perform critical decision making. Fuzzy inference system plays an important role in the artificial intelligence arena. So this paper utilized Mamdani fuzzy inference system to evaluate new drug candidates in efficient way by considering not only safety and efficacy, but also the hottest issue—cost. Though there have been studies relevant to decision making regarding drugs in medical institutions, none have utilized fuzzy computation approaches. The process this paper utilized here was also based on consensus of Drugs and Therapeutic Committee. Further more, the verification and comparison of this paper provide an intuition for system development and further researches.

Keywords: fuzzy logic, drug, healthcare

1. Introduction

The Bureau of National Health Insurance sets several regulations to control medical expenditure since the implementation in 1995. And it is also worldwide for health care providers to contain cost and 'value-for-money' in policy [1]. To choose most effective and safe medicine, therefore, is becoming crucial. It is interesting in how the decision is made for acceptance or rejection of drugs in medical institution. In Taiwan, and also in other countries, almost every hospital has its own Drugs and Therapeutic Committee (DTC or 'Pharmacy and Therapeutic Committee' [2]) to evaluate which new drug could be included in regular formulary (Cotter, Barber, & McKee, 1994). Typically, physicians would not choose expensive drugs when cheaper ones with similar efficacy exist. Physicians' prescribing behavior was defined as 'surrogate shopper' in article (Hollander and Rassuli, 1999). That is, physicians prescribe, but actually, patients take medicine. The fundamental decision making processes are similar. In addition, surrogates may be grated power to make decisions by societal mandate or through institutional forces [3]. DTC, therefore, play an important role of decision maker.

2. Preliminaries

MCDM is the study of methods and procedures in which multiple criteria can be formally incorporated into management planning process [4]. MCDM consists a set of alternatives among which decision-makers have to select or rank. There are many methods for decision making such as analytic hierarchy process (AHP, Satty, 1980), technique for order preference by similarity to ideal solution (TOPSIS, Hwang and Yoon, 1981), etc. And there are many fuzzy MCDM methods as well.

2.1. Fuzzy logic

Linguistic variables are used widely in our daily life such as "cold", "hot ", "high" and "low". Almost everyone is familiar with this form of expression. Only utilize linguistic variables on decision-making could lead to misunderstanding. However, Zadeh(1965) proposed fuzzy set theory, and Bellman and Zedeh(1970) described the decision making method in terms of fuzzy theory. Fuzzy logic, therefore, is gaining more and more popularity because of its characteristics of easy to understand, flexibility, tolerance of imprecise information, and based on natural language.

A fuzzy number is fuzzy set $\tilde{A}$ on R that possesses the following three properties:

1. $\tilde{A}$ is a normal fuzzy set;
2. The α-cut $\tilde{A}^{\alpha}$ of $\tilde{A}$ is a closed interval for every $\alpha \in (0,1]$;
3. The support of $\tilde{A}$ is bounded

And fuzzy number is a fuzzy subset in the universe of discourse X that is both convex [5,6] and normal [7,8]. The α -cut is defined as:

$$\tilde{A}^{\alpha} = \left\{ x \middle| \mu_{\tilde{A}}(x) \geq \alpha \right\}$$

A triangular fuzzy number $\tilde{A} = (a_1, a_2, a_3)$, where $a_1 \leq a_2 \leq a_3$, the membership function is defined as:

$$\mu_{\tilde{A}}(x) = \begin{cases} 0, & x < a_1 \\ (x - a_1)/(a_1 - a_2), & a_1 \leq x \leq a_2 \\ (a_3 - x)/(a_2 - a_3), & a_2 \leq x \leq a_3 \\ 0, & x > a_3 \end{cases}$$

A trapezoidal fuzzy number $\tilde{A} = (a_1, a_2, a_3, a_4)$, where $a_1 \leq a_2 \leq a_3 \leq a_4$, the membership function is defined as:

$$\mu_{\tilde{A}}(x) = \begin{cases} 0, & x < a_1 \\ (x - a_1)/(a_1 - a_2), & a_1 \leq x \leq a_2 \\ 1, \quad a_2 \leq x \leq a_3 & \\ (a_4 - x)/(a_4 - a_3), & a_3 \leq x \leq a_4 \\ 0, & x > a_4 \end{cases}$$

This study utilizes trapezoidal fuzzy numbers. The linguistic weighting variables, linguistic rating variables and corresponding fuzzy numbers are shown as Table1.

If $\tilde{A} = (a_1, a_2, a_3, a_4)$ and $\tilde{B} = (b_1, b_2, b_3, b_4)$ are two positive trapezoidal fuzzy numbers, then $\tilde{A} \oplus \tilde{B} = (a_1 + b_1, a_2 + b_2, a_3 + b_3, a_4 + b_4)$ [9], then the average of $\tilde{A}i$ (i = 1,2…n) can be as the follows.

$$\frac{1}{n}\left(\sum_{i=1}^{n} a_{i1}, \quad \sum_{i=1}^{n} a_{i2}, \quad \sum_{i=1}^{n} a_{i3}, \quad \sum_{i=1}^{n} a_{i4} \right)$$

And the defuzzification value of trapezoidal fuzzy number $\tilde{A} = (a_1, a_2, a_3, a_4)$ is defined to be $(a_1 + a_2 + a_3 + a_4)/4$ [7,10]

Table1. The linguistic variables with corresponding trapezoidal fuzzy number

For importance weighting and rating

Linguistic weighting variable	Corresponding trapezoidal fuzzy number
Very Low (VL)	(0.0, 0.0, 0.1, 0.2)
Low (L)	(0.1, 0.2, 0.2, 0.3)
Medium Low (ML)	(0.2, 0.3, 0.4, 0.5)
Medium (M)	(0.4, 0.5, 0.5, 0.6)
Medium High (MH)	(0.5, 0.6, 0.7, 0.8)
High (H)	(0.7, 0.8, 0.8, 0.9)
Very High (VH)	(0.8, 0.9, 1.0, 1.0)

2.2. Mamdani fuzzy inference

The components of fuzzy Mamdani algorithm are input, output and rules (Mandani et al, 1975). Mamdani's fuzzy inference method is one of the most commonly seen fuzzy methodologies. Mamdani's effort was based on Loft Zadeh's fuzzy algorithms for decision process and complex systems. The basic structure is drawn as Fig 1. Information flows from left to right and aggregate the outputs of rules. The last step is defuzzification.

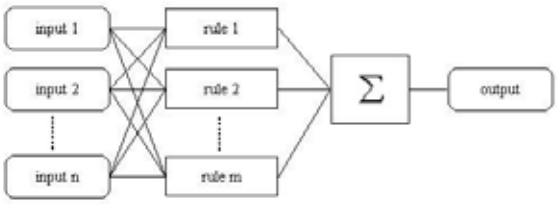

Fig 1. The process fuzzy inference

The Mamdani fuzzy inference uses crisp value as input and aggregates every membership function from rules. The final membership function is then defuzzified with centroid method.

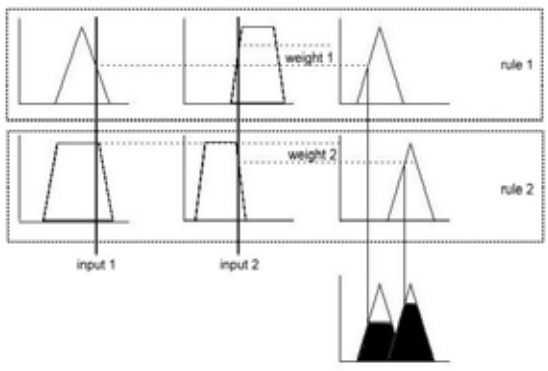

Fig 2. Mamdani's fuzzy inference system

2.3. Delphi Method

Delphi method is group decision process about the likelihood that certain events will occur. This method nowadays has been applied in many fields such as environmental, marketing and sales forecasting. In original Delphi process, the process consists only three components: structuring of information flow; feedback to the participants; and anonymity for the participants. Fowles (1978) further described the following steps for the Delphi method:

1. Forming a team to undertake and monitor a Delphi on a given subject.
2. Selection of panels to participate in the exercise.
3. Developing the first round Delphi questionnaire
4. Testing the questionnaire for proper wording.
5. Transmission of the questionnaires to the team member
6. Analyzing the first round responses.
7. Prepare for the second round questionnaires.
8. Transmission of the second round questionnaires to the panelists
9. Analysis of the second round responses (Steps 7 to 9 are reiterated as long as desired or necessary to achieve consensus in the results.)
10. Preparing a report by the analysis team to present the conclusions of the exercise

3. Criteria of selecting new drugs

The decision-making on selecting new drugs is complex and involves clusters of factors; include the hottest issue—cost (Singer, Martin, Giacomini, & Purdy, 2000). And the decisions making by DTC should base on evidence-based medicine (EBM working Group, 1992). That's why non-scientific forms of evidence are not recorded in literature. [1] Criteria utilized by DTCs are various from hospital to hospital. Some medical intuitions in Taiwan use detail criteria such as pharmacodynamics, pharmacokinetic parameters, adverse reactions, interactions, cost and ease of administrations [11]. Researchers generalize that DTCs make decisions based on evidence of safety, efficacy, cost-effectiveness [2,12], BNHI announced price, and brands [13]. Though, there are many factors that influence physicians' prescribing behavior, this study concerns only criteria during drug selection. After screening on literature and practical process among hospitals, the decision criteria are based on the following three aspects:

Safety: Safety issue involves pharmacodynamics, pharmacokinetics and delivery of drugs. Typically, drugs with broad therapeutic index are better then those with narrow therapeutic index. Adverse effects, contraindications, precautions and elderly patients are also critical considerations [14].

Efficacy: Main ingredients, official indications, dosage form, half-life, frequency of delivery and route of administration are considered by most medical institutions [15 , 16] Equivalency of generic drugs is also an important factor of evaluating efficacy [15, 12]

Cost: Cost seems to be the most important among health care providers. Some medical institutions set up medical expenditure and quality review panel to lower the cost while remain the same quality. Drugs reimbursed by the BNHI are also limited to those listed [17]. Individuals covered by BNHI are required to copay on medicine costs [18]. Thus, health care provider should also consider the copayment that patients would be charged.

4. Methodology

The proposed method was divided into two phases. In first phase, the DTC commits agreement on the rules of choosing drugs. In the second phase, all members of DTC utilize language variables on each criterion and send back to the committee for conclusion.

Phase I (Rules Discovery)

In this phase, DTC members define how many linguistic levels of each criterion and the rules among input and output relationships. Then, make sure each linguistic level should link to any corresponding criteria. There is an example:

"The better the safety is, the higher the priority will gain." in which seven levels of safety is mapping to seven levels of priority. Thus, rules generated:

If "Safety is VeryHigh" then "Priority is VeryHigh"
If "Safety is High" then "Priority is High"
If "Safety is MediumHigh" then "Priority is MediumHigh"
If "Safety is Medium" then "Priority is Medium"
If "Safety is MediumLow" then "Priority is MediumLow"
If "Safety is Low" then "Priority is Low"
If "Safety is VeryHigh"then "Priority is VeryLow"

The process follows the steps of Delphi method. Under the same purpose, the results of this phase can be reused. For example, the DTC want to select three calcium channel block anti-hypertension agents from candidates. They can use former rules, otherwise, the new DTC can build a new set of rules.

Phase II (Evaluation Process)

Step1. DTC, then, collect information on each candidate from all members.

Step2. Calculate the mean of each criterion and the importance weighing of each criterion.
Step3. Utilize Mamdani fuzzy inference algorithm to calculate the priority value; use the defuzzyfied mean of each criterion as input value and consensus rules as inference rules.
Step4. Rank the priority value to allocate the candidates.

5. Verification and comparison

The DTC is arisen for selecting three calcium channel block antihypertensive agents of different ingredient among candidates. The basic information of candidates is shown as Table 2.

In the first phase, the consensus of DTC members can therefore generate rules. There are rules illustrated as Table 3.

The members of the committee seem reluctant to weight the importance of each criterion. Most of the members indicated that all criteria are important equally. In this occurrence, an alternative measurement should apply. Members of the committee were then asked to rank the importance on criteria.

Processes on to the second phase, the linguistic ratings were given on each item and then recorded. Calculate the mean of fuzzy ratings of each candidate as input value.

Step 1. Linguistic variables on each criterion of each item were recorded.
Step 2. Calculate the means. The criteria means of each item were illustrated as Table 4
Step 3. Defuzzy each membership of Table 4 as input of Mamdani's inference system. The fuzzy inference diagram is shown as Fig 3.

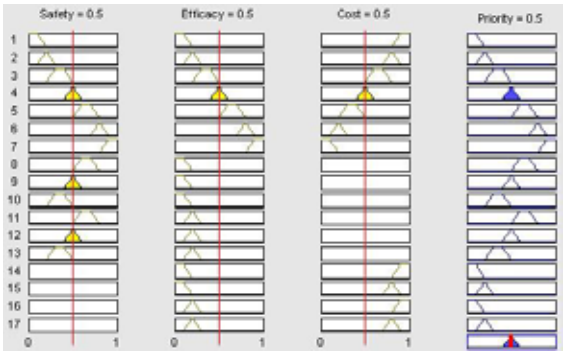

Fig 3. Fuzzy inference diagram

Step 4. Rank the priority value and select 3 candidates of different ingredient. The result is shown in Table 5.

Table 2. Basic information of candidates

Item No.	Ingredient	Dosage	Price	Manufacturer	Dosage form
1	Verapamil HCl	40 MG	2.12	CCPC	Sugar coated
2	Verapamil HCl	240 MG	11.7	YSP	Sustain release
3	Verapamil HCl	80 MG	4.35	YSP	Film coated tablet
4	Verapamil HCl	240 MG	14.5	BASF	Sustain release
5	Verapamil HCl	40 MG	3.33	Abbott	Film coated tablet
6	Nifedipine	5 MG	2.55	YSP	Capsule
7	Nifedipine	10 MG	6.2	YSP	Capsule
8	Nifedipine	10 MG	6.1	CCPC	Capsule
9	Isradipine	5 MG	16.3	Novartis	Capsual
10	Amlodipine (Besylate)	5 MG	14.4	CCPC	Tablet
11	Amlodipine (Besylate)	5 MG	19	Pfizer	Tablet
12	Felodipine	5 MG	16	Genovate	Sustain release
13	Felodipine	5 MG	17.5	Astra	Sustain release

Table 3 The fuzzy inference rules

1. If (Safety is VL) or (Efficacy is VL) or (Cost is VH) then (Priority is VL)
2. If (Safety is L) or (Efficacy is L) or (Cost is H) then (Priority is L)
3. If (Safety is ML) or (Efficacy is ML) or (Cost is MH) then (Priority is ML)
4. If (Safety is M) or (Efficacy is M) or (Cost is M) then (Priority is M)
5. If (Safety is MH) or (Efficacy is MH) or (Cost is ML) then (Priority is MH)
6. If (Safety is H) or (Efficacy is H) or (Cost is L) then (Priority is H)
7. If (Safety is VH) or (Efficacy is VH) or (Cost is VL) then (Priority is VH)
8. If (Safety is MH) and (Efficacy is VL) then (Priority is MH)
9. If (Safety is M) and (Efficacy is VL) then (Priority is M)
10. If (Safety is ML) and (Efficacy is VL) then (Priority is ML)
11. If (Safety is MH) and (Efficacy is L) then (Priority is MH)
12. If (Safety is M) and (Efficacy is L) then (Priority is M)
13. If (Safety is ML) and (Efficacy is L) then (Priority is ML)
14. If (Efficacy is VL) and (Cost is VH) then (Priority is VL)
15. If (Efficacy is VL) and (Cost is H) then (Priority is L)
16. If (Efficacy is L) and (Cost is VH) then (Priority is VL)
17. If (Efficacy is L) and (Cost is H) then (Priority is L)

Table 4. Average membership of each item

Item No.	Safety	Efficacy	Cost
1	(0.44,0.54,0.58,0.68)	(0.04,0.08,0.14,0.24)	(0.02,0.04,0.12,0.22)
2	(0.34,0.44,0.5,0.6)	(0.54,0.64,0.66,0.76)	(0.52,0.62,0.68,0.78)
3	(0.42,0.52,0.54,0.64)	(0.2,0.28,0.36,0.46)	(0.14,0.22,0.3,0.4)
4	(0.34,0.44,0.5,0.6)	(0.54,0.64,0.66,0.76)	(0.64,0.74,0.8,0.88)
5	(0.44,0.54,0.58,0.68)	(0.04,0.08,0.14,0.24)	(0.1,0.16,0.24,0.34)
6	(0.64,0.74,0.8,0.88)	(0.5,0.6,0.64,0.74)	(0.12,0.16,0.24,0.34)
7	(0.68,0.78,0.82,0.9)	(0.74,0.84,0.88,0.94)	(0.34,0.44,0.5,0.6)
8	(0.68,0.78,0.82,0.9)	(0.74,0.84,0.88,0.94)	(0.34,0.44,0.5,0.6)
9	(0.6,0.7,0.72,0.82)	(0.74,0.84,0.88,0.94)	(0.64,0.74,0.8,0.88)
10	(0.74,0.84,0.88,0.94)	(0.72,0.82,0.9,0.94)	(0.64,0.74,0.8,0.88)
11	(0.74,0.84,0.88,0.94)	(0.76,0.86,0.92,0.96)	(0.74,0.84,0.94,0.96)
12	(0.74,0.84,0.88,0.94)	(0.72,0.82,0.9,0.94)	(0.7,0.8,0.86,0.92)
13	(0.74,0.84,0.88,0.94)	(0.78,0.88,0.96,0.98)	(0.76,0.86,0.92,0.96)

Table 5a. Selected drugs with fuzzy inference system.

Priority value	Item No.	Ingredient	Dosage	Price	Manufacturer	Dosage form
0.71817	7	Nifedipine	10 MG	6.2	YSP	Capsule
0.58375	9	Isradipine	5 MG	16.3	Novartis	Capsule
0.55927	10	Amlodipine (Besylate)	5 MG	14.4	CCPC	Tablet

Table 5b. Selected drugs with simple aggregating method (no weighted).

Priority value	Item No.	Ingredient	Dosage	Price	Manufacturer	Dosage form
2.17500	7	Nifedipine	10 MG	6.2	YSP	Capsule
1.93000	10	Amlodipine (Besylate)	5 MG	14.4	CCPC	Tablet
1.87500	12	Felodipine	5 MG	16	Genovate	Sustain release

From Table 5a and 5b, it is observed that Isradipine (the 9th item) has higher price and is selected by fuzzy inference system. The fuzzy inference system has already considered the importance of each criterion while simple aggregation has not. Therefore, it could be unnecessary to weight the importance of criteria. But it still needs further evaluations to confirm that.

6. Conclusion

The fuzzy logic concept has been utilized not only in the multiple criteria decision making arena, but also in medical device controlling and as well as in pharmacological applications [19]. Advanced computation power makes the complex inferences possible. And this paper shows the feasibility of adopting drugs by fuzzy inference system.

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