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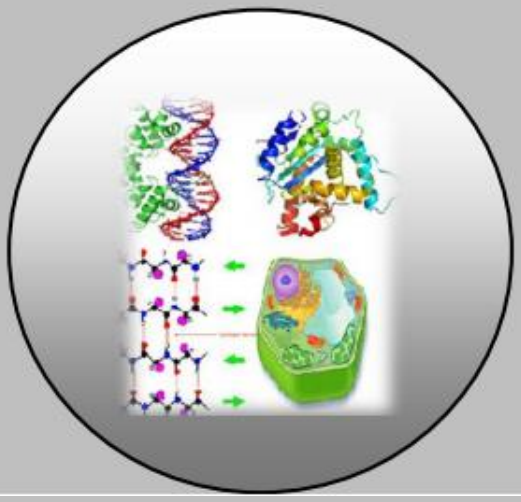

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RESEARCH PAPER

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Introducing A Fuzzy Scale Based Model for Measuring Medicinal Drug Properties with Reference to the Varying Patient Conditions

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ABSTRACT

There involve many factors in choosing a proper treatment. Once someone have selected the appropriate medicine, the choice of the appropriate doses and the administration in the proper interval is important for the most successful use of the drug. At present, the decision systems available for drug selection are based on numerical data and quantitative properties of drugs, while the immeasurable qualities like Safety Profile, side/adverse effect or mode of action play much important role in drug effectiveness. So it requires an improve decision support system that includes immeasurable qualities of drug. A fuzzy scaled based system can support the practitioner to help to choose the best drug/combination of drugs.

Keywords: Fuzzy Scaled Based Model, Quantitative Properties and Medicinal Drug.

INTRODUCTION

Decision making in medicine is the most important part for any practitioner. Choosing a suitable drug or combination of drugs is always a difficult task for medical practitioners. In many cases it is challenging and controversial process. The qualities of the "best medicine" is difficult to judge and difficult to measure and often immeasurable.

At present, the decision systems available for drug selection are based on numerical data and quantitative properties of drugs. A range of quantitative models are used to analyze, combine and interpret data in different areas of health-care research. For example, the Survival models of statistics deals with death in biological organisms and failure in mechanical systems. One example of survival models is a Cox proportional hazards model [Cox, 1972]. But the complexity of biomedical systems makes inappropriate the traditional quantitative approaches of analysis and design.

When dealing with such systems, there is almost an unavoidable significant degree of subjectivity or fuzziness when describing their behavior and analyzing their characteristics or either it requires quantifying those variables. The quantification of phenomenon related to humankind is too complicated to be obtained precisely. In fact, almost all theories of medical sciences characterize the real world in an approximate manner. For example, the paper of Oguntade and Besumont [Oguntade and Beaumont, 1982] examines the possibility of handling treatment effects as a fuzzy relational problem with particular reference to ophthalmology. The same is true for immeasurable qualities of medicine/drugs like Safety Profile, side/adverse effect or mode of action. These subjective/fuzzy qualities play much important role in drug effectiveness. So it requires an improve decision support system that includes immeasurable qualities of drug. A fuzzy mathematical theory based system can support the practitioner to help to choose the best drug/combination of drugs.

THE FUZZY MATHEMATICS

Fuzzy mathematics is a branch of mathematics developed by Lotfi Asker Zadeh [Zadeh, 1965] deals with the sets with unclear (fuzzy) boundary. Esogbue and Elder [1983] showed superiority of fuzzy diagnosis model over Classical mathematical models for medical diagnosis, which have been computerized, are known to perform very poorly when compared to diagnoses made by the physician. They described in a study that fuzzy diagnosis models were computerized, validated and compared with a mock physician hypothesis as well as existing mathematical models.

THE IMMEASURABLE QUALITIES OF DRUG

On the basis of available literature and discussions with medical practitioners, It can be compiled various drug qualities. Many of them can be measured quantitatively, but the actual nature of each drug quality is subjective and a fuzzy scale is much better for their measurement. When evaluating new treatments in clinical researches, it is useful to consider the effects of such qualities jointly.

The remarkable qualities of drugs are given as follows, and can be measured on a fuzzy scale with range 0 to 1, where 0 represents the worst and 1 represents the best. The fuzzy scale variable represents the particular quality is given in bracket.

1. Efficacy of Drug (X_1): According to the expert's (doctor's) opinion, this is the most important property of the drug. For example in a study by Maiti et.al. [2011] on the comparative study of efficacy and safety of two drugs Olopatadine hydrochloride and rupatadine fumarate in seasonal allergic rhinitis it is to be concluded that Olopatadine is a better choice in SAR in comparison to rupatadine due to its better efficacy and safety profile.

2. Safety Profile of Drug (X_2) : According to the expert's (doctor's) opinion, this is the second most important property of any drug. For example in a study conducted by Hwang et.al. [2012] on comparing adverse drug reaction profiles of two tacrolimus formulations Tacrobell(®) (TB) and Prograf(®) (PG) in rats, it is seen that TB is similar to PG in terms of nephrotoxicity, hepatoxicity and diabetogenic effect.

3. Drug Side/Adverse effects (X_3) : Many drugs considered to be bad choice for practitioners due to their side/adverse effects. For example Youngwoon et.al. [2012] reported a case of drug-induced hepatitis (severe hepatotoxicity) due to Bortezomib in Multiple Myeloma
4. Onset of Action (X_4) : It is very important for emergency treatments. For example study of Han et.al. [2011] on comparison of two treatments azelastine nasal spray 0.1% (ANS) versus levocabastine nasal spray 0.05% (LNS) in patients with moderate-to-severe allergic rhinitis it is seen that there is a higher symptom relief rate in the LNS group than in the ANS group within 30 min of administering the first dose.
5. Tolerability of Drug (X_5) : Drug tolerance is commonly encountered in pharmacology, when a subject's reaction to a specific drug and concentration of the drug is progressively reduced. For example A study by Yusuf et.al. [2012] showed that the full-dose polycap (plus K (+) supplementation) reduces BP and low-density lipoprotein cholesterol to a greater extent compared with the low dose, with similar tolerability in Individuals at High Risk of Cardiovascular Diseases.
6. Doses and Administration (X_6) : Various dosage forms may exist for a single particular drug, since different medical conditions can warrant different routes of administration. The doses and administration of a drug is taken as fuzzy variable is more feasible than it is taken as numeric variable.
7. Mode of Action (X_7) : (As experts said) It is important to distinguish between actions of drugs and their effects. Actions of drugs are the biochemical physiological mechanisms by which the chemical produces a response in living organisms.
8. Drug Reaction (X_8) : Most of the time, medicines make our lives better. But medicines can also cause unwanted reactions. For example In a study by Michel et.al [2012] about a prescribed analgesic drug flupirtine which is marketed for about 30 years, hepatotoxicity was detected in 31% of patients receiving flupirtine for ≥ 6 weeks.
9. Drug Resistance (X_9) : This is a major concern because a resistant infection may kill, can spread to others, and imposes huge costs to individuals and society.
10. Cost Effectiveness (X_{10}) : In many cases cost-effectiveness of drug therapy is a major consideration for selection of treatment because of patient affordability.
11. Drug Interactions (X_{11}) : Interactions can change the actions of one or both drugs. The drugs might not work, or we could get side effects. Sometimes drug interactions with other drugs and disease severity may lead confounding effect, as Fang et.al. [2012] said "confounding by indication is a vexing problem, especially in evaluating treatment effects using observational data, since treatment decisions are often related to disease severity, prognosis, and frailty."
12. Peak Aqueous Concentration of Drug (X_{12}) : Sometimes an increase in local activity of the drug with an increase in the drug concentration in the aqueous humor would favor a reduction in the risk of infections etc. after surgery.
13. Spectrum of Activity (X_{13}) : (As experts said) Spectrum of activity defines the range of pathogens which are sensitive to a fungicide, for instance a fungicide may be broad spectrum and can then be used to control many different pathogens, e.g. MBC benzimidazole fungicides, or it may have a narrow spectrum of activity affecting only a few pathogens, e.g. phenylamides, which have activity against oomycete fungi such as Phytophthora, Pythium spp. and the downy mildews.

14. Pharmacokinetics (X_{14}) : According to the medical dictionary, pharmacokinetics is the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body. Isbister et.al.[2012] studied two infusion rates of antivenom for treatment of non-pregnant adult patients through randomized controlled trial and concluded that the slower infusion rate would not reduce the rate of severe systemic hypersensitivity reactions from current high rates.

The aforesaid fourteen qualities of drugs are remarkable and important in any medicinal decision model for the selection of best treatment. When choosing among established treatments for an individual patient, or when evaluating new treatments in clinical researches, it is useful to consider the effects of such qualities jointly. For example the usefulness of aspirin for its analgesic effects and its ability to lower the risk of cardiovascular disease is also counted for the risk that aspirin may cause a stomach problems. Beta blockers effectively reduce abnormally high blood pressure but in parallel also cause dizziness, fatigue, insomnia or a reduced libido.

THE DRUG EFFECT MODEL

a. Making the Drug Effect Vector

Let for a particular disease, the available treatment alternatives are

M_α ($\alpha = 1, 2, ..., m$) .....(1)

Where *m* (The number of available treatment alternatives) is depend on the particular disease. It should be noted that M_α is either a drug molecule (Rx) or a combination of drug molecules or a procedure to treat.

Now, $M_\alpha = M_\alpha \left(X_1, X_2, ... \right)$ .....(2)

That is, all M_α's are the functions of drug effect variables X_1, X_2,…

Where X_1 is the variable associated with drug efficacy, X_2 is the variable associated with safety profile, and so on.

Therefore X_j (j = 1,2,…) represents the j^{th} quality of the drug.

Each drug property X_j (j=1,2,…) is a fuzzy variable having values in the range $\left[X_j^l, X_j^u \right]$ with some associated membership function x_j of the form

$$\left[X_j^l, X_j^u \right] \xrightarrow{x_j} [0,1] \quad .....(3)$$

If the variable X_j has the lowest value X_j^l in the range, it means that its membership function x_j has the value 0 (zero). On the other hand if the variable X_j has the highest value X_j^u in the range, it means that its membership function x_j has the value 1 (one). For all the other values of X_j the membership function x_j has a value between 0 and 1. The basic assumption for all the drug qualities is that it can be scaled into worst to best range. That is X_j has value X_j^l as 'worst' and value X_j^u as 'best' with corresponding value x_j between 0 and 1.

For example consider the variable X_1, the efficacy of the drug. It has the values in the range $\left[X_1^l, X_1^u\right]$ with associated (real valued) membership function x_1, where X_j^l means nil efficacy with $x_1 = 0$ and X_j^u means perfect efficacy with $x_1 = 1$.

All the above drug properties can be represented by a fuzzy vector

$$M_\alpha = \left[X_1 \;\; X_2 \;\ldots\; X_{14}\right]^{\mathrm{T}} \qquad \ldots\ldots(4)$$

with corresponding membership function

$$m_\alpha = \left[x_1 \;\; x_2 \;\ldots\; x_{14}\right]^{\mathrm{T}} \qquad \ldots\ldots(5)$$

We called the vector $M_\alpha = \left[X_1 \;\; X_2 \;\ldots\; X_{14}\right]^{\mathrm{T}}$ the Effect Vector.

For making effect vector, it is required to evaluate their membership function. There are many methods available in literature for making membership function of a fuzzy variable. We presented here one methods 'Saaty's Eigenvector method' and 'Interpolation Method'.

a.1 Saaty's Eigenvector method

Saaty's Eigenvector method is actually the modified least squares method. Let A_1, A_2, …, A_n be the members of fuzzy set. We are interested in evaluating the membership values of the above members. Saaty [1977] proposed to use a matrix A of rational numbers taken from the set $\left\{\frac{1}{9}, \frac{1}{8}, \ldots, 1, 2, \ldots, 8, 9\right\}$. Each entry of the matrix A represents a pairwise judgement. That is the entry a_{ij} of A denotes the number that represents the relative membership of element A_i when it is compared with element A_j. Obviously $a_{ij} = 1/a_{ji}$ and $a_{ii} = 1$.

Let us first examine the case (consistent case) in which it is possible to have perfect values a_{ij}. Now we have $a_{ij} = \frac{m_i}{m_j}$, where m_i denotes the actual membership value of member A_i.

So that

$$a_{ij} = a_{ik}a_{kj}\,,\; i,j,k = 1,2,3,\ldots,n \qquad \ldots\ldots(6)$$

where n is the number of elements in the fuzzy set.

It can be proved that A has rank 1 with $\lambda - n$ to be its nonzero Eigen-value. Then we have

$$A_x = nX \qquad \ldots\ldots(7)$$

Where X is an Eigen vector. From the fact that $a_{ij} = \frac{m_i}{m_j}$, the following are obtained :

$$\sum_{j=1}^{n} a_{ij} m_j = \sum_{j=1}^{n} m_i = n m_i \;;\; i = 1,2,\ldots,n \qquad \ldots\ldots(8)$$

or,

$$AM = nM. \qquad \ldots\ldots(9)$$

Equation (9) states that n is an Eigen value of A with M a corresponding Eigen vector. In the non-consistent case, the pairwise comparisons are not perfect. That is the entry a_{ij} might deviate from the real ratio m_i/m_j.

In order to find the membership values in the non-consistent case, one should find an Eigen vector that corresponds to the maximum eigenvalue $\lambda_{\max}$. That is to say to find the principal Eigenvector *M* that satisfies

$AM = \lambda_{\max} M$, where $\lambda_{\max} = n$. .....(10)

b. Disease/Patient Properties versus Treatment Effects

Further treatments effects are related with disease/patient properties say duration, intensity or complications. The disease properties are again fuzzy variables, and can have the values for example as High, Low, Normal, Very Low, Very High and so on.

On the basis of available literature, disease/patient properties for a particular disease α may be categorize into two parts

a.) Disease/patient properties those are treatment independent, say patient age/gender, duration of disease, complications present, previous histories, family history etc. Let we denote it by $I_1, I_2, ..., I_p$.'s , the *p* fuzzy variables and can be modified using expert (doctor's) interventions, in the sense that experts can decide which variable are included for α.

An example is the study by Yuequan et.al [2010] on prognostic factors and family history for survival of esophageal squamous cell carcinoma patients after surgery suggested that Family history of esophageal cancer is an important prognostic factor that surgeons should take into consideration when selecting a treatment method.

Another example is the study of Ralevski et.al. [2010] on analgesic effects of ethanol. In this study they concluded that neuroticism and family history of alcoholism both influence the analgesic response of alcohol.

After finalizing $I_k^{'s};\ k = 1, 2, ..., p$'s for a particular disease, the real condition of the disease in a particular patient is represented by the fuzzy vector

$I = [I_1, I_2, ..., I_p]^T$ ……(11)

With corresponding membership vector

$i = [i_1, i_2, ..., i_p]^T$ ……(12)

$i_k \in [0,1];\ k = 1, 2, ..., p$

Where we can say

$i_k \to 1,$ for a better condition

and

$i_k \to 0,$ for a worst condition

It should be noted that if i_k is some patient characteristics say age or gender then we called it 'worst' if it is a high risk group (having higher probability) for the disease say older age or 'male' (say for hemophilia).

These properties are essential to make initial steps to take decision about treatment. So we called *I* as Information Vector. For the information vector, there exists a one way relation between *I* and the treatment properties.

i.e. $I_k \to X_i$, for some *i*; *i* =1,2,…,14; *k* =1,2,...,*p*

Since both sides of the relations are the fuzzy variables, therefore these relations can be evaluated using fuzzy rules. One good technique is to show the relation between I_p and X_i by a matrix of the form

$$\begin{array}{c} \\ i_1 \\ i_2 \\ . \\ i_p \end{array} \begin{array}{c} \begin{array}{cccc} x_1 & x_2 & \ldots & x_{14} \end{array} \\ \begin{bmatrix} \alpha_{11} & \alpha_{12} & \ldots & \alpha_{1,14} \\ \alpha_{21} & \alpha_{22} & \ldots & \alpha_{2,14} \\ . & . & \ldots & . \\ \alpha_{p1} & \alpha_{p1} & \ldots & \alpha_{p,14} \end{bmatrix} \end{array}$$

We called it the Information Matrix $A_{p\times 14}$. The basic assumption here making for the information matrix is that the relationship between the information variable and the drug quality variable is a constant positive value for each combination of information-drug quality variables. However in general case it may be variable.

The fuzzy values of drug qualities will be changed on disease conditions or states of the disease. Assuming that old drug qualities and disease influenced drug quality changes are additive in nature, a new membership function for drug qualities is evaluated by the formula

$$\begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{\text{improved by } I} = \begin{bmatrix} x_1 \\ x_2 \\ . \\ x_{14} \end{bmatrix}_{\text{General}} + \begin{bmatrix} \alpha_{11} & \alpha_{12} & \ldots & \alpha_{1,14} \\ \alpha_{21} & \alpha_{22} & \ldots & \alpha_{2,14} \\ . & . & \ldots & . \\ \alpha_{p1} & \alpha_{p2} & \ldots & \alpha_{p,14} \end{bmatrix}^T \begin{bmatrix} i_1 - 0.5 \\ i_2 - 0.5 \\ . \\ i_p - 0.5 \end{bmatrix} \quad \ldots\ldots(13)$$

or in usual notations

$$X_{\text{improved by } I} = X_{\text{General}} + A^{\mathrm{T}} I - A^{\mathrm{T}} I_{0.5} \quad \ldots\ldots(14)$$

Where $I_{0.5}{}^{\mathrm{T}} = \begin{bmatrix} 0.5 & 0.5 & \ldots & 0.5 \end{bmatrix}$

subject to :

$x_j > 1 \Rightarrow x_j = 1$

and

$x_j < 0 \Rightarrow x_j = 0 \;;\; j = 1,2,\ldots,14$

It should be noted that

X_{General} are the observed qualities of the drug at $I = I_{0.5}$

b.) Disease properties those are treatment dependent, say intensity of disease, health recovery or complications initiated during treatment. We called these properties 'conditions'. Let we denote the 'conditions' by $D_1, D_2, \ldots, D_q$.

For example in a study by Budzynski et.al. [20] in patients with coronary artery disease, it is shown that double dose of omeprazole significantly decreased symptoms severity in 35% of patients with coronary artery disease, as well as frequency of some electrocardiographic signs of myocardial ischaemia during stress test.

Another example is the study on Chinese medicine treatment of non-acute bronchial asthma complicated by gastroesophageal reflux by Zhao et.al. [97] where it is shown that the clinical symptoms of non-acute asthma complicated by gastroesophageal reflux can be improved by some Chinese drugs. Curative effects can be increased by combining the use of Traditional Chinese medicine with Western medicine.

After finalizing $D_k^{'s};\ k=1,2,...,q$'s for a particular disease, the real condition of the disease in a particular patient is represented by the fuzzy vector called 'condition vector'

$D = [D_1, D_2,..., D_q]^T$ ……(15)

With corresponding membership vector

$d = [d_1,d_2,...,d_p]^T$ ……(16)

$d_k \in [0,1];\ k=1,2,...,q$

Without loss of generality, we can write

$d_k \to 1,$ if condition improves

and

$d_k \to 0,$ if condition worsen

For these properties there exists a two way relation between disease property and the treatment property

i.e. $D_k \rightleftarrows X_i$, for some *i*; *i* =1,2,…,14; *k* =1,2,...,*q*

Since both sides of the relations are the fuzzy variables, therefore these relations can be evaluated using fuzzy rules.

D_k's are the fuzzy variables and modifiable using expert (doctor's) interventions, in the sense that experts can decide which variable are included for α and what are the values (in the fuzzy sense) of those variables in a particular condition.

The mathematical representation of $D_k \rightleftarrows X_i$ is more difficult than the representation of $I_k \to X_i$, because every side is influenced by the other side simultaneously. A time dependent dynamic model is useful for representing such relation. Let *T* be the time set with starting time 0 and then 1, 2, 3...,*t*,*t*+1,... and so on. Let the fuzzy interactions between disease properties (conditions) and drug/treatment qualities are represented by the matrix

$$\begin{array}{c} \\ d_1 \\ d_2 \\ . \\ d_q \end{array}\begin{array}{c} \begin{array}{cccc} x_1 & x_2 & ... & x_{14} \end{array} \\ \begin{bmatrix} \beta_{11} & \beta_{12} & ... & \beta_{1,14} \\ \beta_{21} & \beta_{22} & ... & \beta_{2,14} \\ . & . & ... & . \\ \beta_{q1} & \beta_{q1} & ... & \beta_{q,14} \end{bmatrix} \end{array}$$

We called it the Condition Matrix $B_{q\times 14}$. The basic assumption here making for the condition matrix is that the relationship between the condition variable and the drug quality variable is a constant value for each combination of condition-drug quality variables. However in general case it may be variable.

CONCLUSION

After making the drug effect vector with corresponding membership function and the Disease/patient properties, the tools for the medicinal drug functioning is available for further study. After that a more precise algorithmic format of the model makes it easy to apply the practical, decision-making approaches used by practitioners in daily practice.

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