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Application of the Fuzzy Theory to Drug Effects

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Drug effects are described in terms of fuzzy sets; practical application to simple cases gave reasonable results.

Keywords fuzzy set; drug effect; fuzzy vector; fuzzy matrix

Fuzzy set theory[1] has been practically applied[2,3] in the fields of automatic control technics and medical diagnosis,[4,5] among others. The theory can associate poorly defined (fuzzy) descriptions[6] with mathematical variables. Such descriptions are common in connection with pharmaceutical effects and drug actions, but little research in this area has been reported.

The purpose of the present paper is to derive equations to represent the relation of symptoms and drug effects. The obtained equations are applied to various examples using fuzzy vectors and fuzzy matrices.

Theoretical

We intend to develop a mathematical description of drug effects and symptoms. Our discussion does not take account of the influence of dosage form, the method of preparation and so on, but only the intrinsic drug effects.

We can regard drug effects as a state consisting of the drug operation and symptoms. Thus we suppose that the drug effects set ($\Delta \boldsymbol{X}$) is equal to the common set of the drug operation set ($\boldsymbol{H}$) and the symptoms set ($\boldsymbol{X}$).

The relation is as follows:

$$\Delta \boldsymbol{X}=\boldsymbol{H}\cap \boldsymbol{X} \tag{1}$$

The sets satisfying Eq. 1 are not always one set. The desired set is the maximum set that contains all subsets satisfying Eq. 1. This is written in the following abbreviated form

$$\Delta \boldsymbol{X}=\boldsymbol{H}\circ \boldsymbol{X} \tag{2}$$

In the fuzzy theory, Eq. 2 can be expressed in the functional form

$$f(\boldsymbol{X})=\boldsymbol{H}\circ \boldsymbol{X} \tag{3}$$

and the converse fuzzy relation is given by

$$f^{-1}(\boldsymbol{X})=\boldsymbol{X}\circ \boldsymbol{H} \tag{4}$$

The fuzzy sets are defined by membership functions which allow Eqs. 2 and 3 to be calculated explicitly.

We define positive effects as drug effects operating for the better, and negative effects as those for the worse. We will proceed to the discussion of positive drug effects and negative drug effects individually.

Positive Drug Effects The region of the symptoms set is decreased by positive drug effects. Thus we have

$$\boldsymbol{X}_{\mathrm{f}}=\boldsymbol{X}-\Delta \boldsymbol{X} \tag{5}$$

were $\boldsymbol{X}_{\mathrm{f}}$ represents the final symptoms after dosing.

Using the complement set $\overline{\Delta \boldsymbol{X}}$ of $\Delta \boldsymbol{X}$, Eq. 5 becomes:

$$\boldsymbol{X}_{\mathrm{f}}=\boldsymbol{X}\cap \overline{\Delta \boldsymbol{X}} \tag{6}$$

From Eq. 2, $\Delta \boldsymbol{X}$ is given by

$$\Delta \boldsymbol{X}=\boldsymbol{H}\circ \boldsymbol{X} \tag{7}$$

Equations 6 and 7 are the formulae for positive drug effects. By using the membership function, Eqs. 6 and 7 become as follows[1]:

$$x(f)_i=\min[x_i, \overline{\Delta x_i}] \tag{8}$$

$$\Delta x_i=\max[\min(x_{ij}, x_j)] \tag{9}$$

where $x(f)_i$ and Δx_i are elements of $\boldsymbol{X}_{\mathrm{f}}$ and $\Delta \boldsymbol{X}$, respectively, and x_{ij} are elements of $\boldsymbol{H}$. The max represents the maximum among variables indexed by j, and min is similar. The usual representation $\mu_{\boldsymbol{X}}(x_i)$ for membership functions is written as x_i in this paper.

Let us consider examples to test the validity of Eqs. 6 and 7. We shall take symptoms with four kinds of degree. Thus we need a 4-dimensional vector (fuzzy vector) for $\boldsymbol{X}$ as follows:

$$\boldsymbol{X}=[x_1, x_2, x_3, x_4] \tag{10}$$

where x_j ($j=1$—4) corresponds to the degree of symptoms. The severity increases in the order of x_1, x_2, x_3 and x_4. Thus x_1 describes very slight symptoms and x_4 the worst.[3]

When we use Eqs. 7 or 9, we must array the elements of $\boldsymbol{X}$ as follows:

$$\boldsymbol{X}=[x_a, x_b, x_c, x_d] \tag{11}$$

where $x_a \leqq x_b \leqq x_c \leqq x_d$, and a<b<c<d for equality, because Eq. 2 includes this condition.

We use the 4×4 matrix (fuzzy matrix) for $\boldsymbol{H}$ as follows:

$$\boldsymbol{H}=\begin{bmatrix} x_{11} & x_{12} & x_{13} & x_{14} \\ x_{21} & x_{22} & x_{23} & x_{24} \\ x_{31} & x_{32} & x_{33} & x_{34} \\ x_{41} & x_{42} & x_{43} & x_{44} \end{bmatrix} \tag{12}$$

Thus $\Delta \boldsymbol{X}$ is also a 4-dimensional vector as follows:

$$\Delta \boldsymbol{X}=[\Delta x_1, \Delta x_2, \Delta x_3, \Delta x_4] \tag{13}$$

Let us give values of x_j ($j=1$—4) as follows:

$x_1=0$, $x_2=0.3$, $x_3=0.7$ and $x_4=1$

Thus we use the following initial symptoms

$$\boldsymbol{X}=[0, 0.3, 0.7, 1] \tag{14}$$

As an example we set $\boldsymbol{H}$ as follows:

$$\boldsymbol{H}=\begin{bmatrix} 0.3 & 0.6 & 0.9 & 0.4 \\ 0 & 0.3 & 0.6 & 0.9 \\ 0 & 0 & 0.3 & 0.6 \\ 0 & 0 & 0 & 0.3 \end{bmatrix} \tag{15}$$

From Eqs. 9, 14 and 15, we get Δx_j ($j=1$—4) as follows:

$$\Delta x_1 = \max[\min(0, 0.3), \min(0.3, 0.6), \min(0.7, 0.9), \min(1, 0.4)]$$
$$= \max[0, 0.3, 0.7, 0.4] = 0.7$$

similarly

$$\Delta x_2 = 0.9, \quad \Delta x_3 = 0.6, \quad \Delta x_4 = 0.3$$

Thus

$$\Delta \boldsymbol{X} = [0.7, 0.9, 0.6, 0.3] \tag{16}$$

The elements of $\overline{\Delta \boldsymbol{X}}$ are obtained by subtracting the elements of $\Delta \boldsymbol{X}$ from one.

$$\overline{\Delta \boldsymbol{X}} = [0.3, 0.1, 0.4, 0.7] \tag{17}$$

From Eqs. 8, 14 and 17, we get final symptoms $\boldsymbol{X}_f$ as follows:

$$\boldsymbol{X}_f = [\min(0, 0.3), \min(0.3, 0.1), \min(0.7, 0.4), \min(1, 0.7)]$$
$$= [0, 0.1, 0.4, 0.7] \tag{18}$$

The symptoms are improved because $\boldsymbol{X}_f \leqq \boldsymbol{X}$.

Now we use the most effective drug and a non effective drug as examples to check the assumptions. We use Eq. 14 for the initial symptoms. In the present representation of symptoms, the most effective drug will have the following $\boldsymbol{H}$

$$\boldsymbol{H} = \begin{bmatrix} 1 & 1 & 1 & 1 \\ 0 & 1 & 1 & 1 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \end{bmatrix} \tag{19}$$

Similarly to the previous example, we obtain:

$$\Delta \boldsymbol{X} = [1, 1, 1, 1] \tag{20}$$

$$\overline{\Delta \boldsymbol{X}} = [0, 0, 0, 0] \tag{21}$$

$$\boldsymbol{X}_f = [0, 0, 0, 0] \tag{22}$$

Thus the symptoms disappear completely, as expected.

If symptoms such as $x_1 = 0$, $x_2 = 0.7$, $x_3 = 1$ and $x_4 = 0.3$ are used, the elements must be rearranged as $[x_1, x_4, x_2, x_3]$ only when $\boldsymbol{X}$ is operated to $\boldsymbol{H}$. The reason is due to Eq. 2, and is also shown in Eq 11.

A non effective drug will have the following $\boldsymbol{H}$

$$\boldsymbol{H} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{23}$$

Similarly to the above examples, we get:

$$\boldsymbol{X}_f = [0, 0.3, 0.7, 1] \tag{24}$$

The result shows that the drug is ineffective because $\boldsymbol{X}_f = \boldsymbol{X}$.

Negative Drug Effects Negative drug effects work in the opposite direction to positive drug effects. Thus, we suppose that negative drug effects are represented by the converse fuzzy relation (Eq. 4) of the relation for positive drug effects (Eq. 3). Furthermore, negative drug effects increase the region of the symptoms set.

From these points of view, we employ the following equation for negative drug effects

$$\boldsymbol{X}_f = \boldsymbol{X} \cup \Delta \boldsymbol{X} \tag{25}$$

$$\Delta \boldsymbol{X} = \boldsymbol{X} \circ \boldsymbol{H} \tag{26}$$

Similarly for positive drug effects, we get

$$x(f)_i = \max[x_i, \Delta x_i] \tag{27}$$

$$\Delta x_i = \max[\min(x_j, x_{ji})] \tag{28}$$

Let us use the above equation. We use Eq. 14 for the initial symptoms and the following operator $\boldsymbol{H}$

$$\boldsymbol{H} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0.6 & 0 & 0 & 0 \\ 0.9 & 0.6 & 0 & 0 \\ 0.4 & 0.9 & 0.6 & 0 \end{bmatrix} \tag{29}$$

From Eqs. 14, 27 and 29, we get Δx_j ($j=1$—4) as follows:

$$\Delta x_1 = \max[\min(0, 0), \min(0.3, 0.6), \min(0.7, 0.9), \min(1, 0.4)]$$
$$= \max[0, 0.3, 0.7, 0.4] = 0.7$$

similarly

$$\Delta x_2 = 0.9, \quad \Delta x_3 = 0.6, \quad \Delta x_4 = 0$$

Thus

$$\Delta \boldsymbol{X} = [0.7, 0.9, 0.6, 0] \tag{30}$$

From Eqs. 14, 27 and 30, we get

$$\boldsymbol{X}_f = [\max(0, 0.7), \max(0.3, 0.9), \max(0.7, 0.6), \max(1, 0)]$$
$$= [0.7, 0.9, 0.7, 1] \tag{31}$$

The symptoms becomes worse because $\boldsymbol{X}_f \geqq \boldsymbol{X}$.

Next, the worst operator will be as follows:

$$\boldsymbol{H} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 1 & 1 & 1 & 0 \end{bmatrix} \tag{32}$$

Using the above procedure, we get

$$\Delta \boldsymbol{X} = [1, 1, 1, 0] \tag{33}$$

$$\boldsymbol{X}_f = [1, 1, 1, 1] \tag{34}$$

The symptoms become the worst possible.

Conclusion

We have applied the concept of the fuzzy set to drug effects and derived equations relating drug effects and drug operators. We consider that Eqs. 6 and 7, and Eqs. 25 and 26 can adequately represent the elementary relations between the drug and the operation.

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